Chapter 1

Overview of Comorbid Disorders in ADHD

There are thousands of scientific studies examining the comorbidity of psychiatric disorders with attention-deficit/hyperactivity disorder (ADHD), but for the clinician, it is the individual patient that is most important. My colleagues and I (Pliszka, Carlson, & Swanson, 1999) opened our previous work on this topic with the case of Justin:

Justin was a 13-year-old seventh grader. He was first diagnosed with ADHD when he was 5 years of age. His doctor prescribed methylphenidate, which led to increased agitation. He was managed without medication until the age of 7, when his severe hyperactivity and aggression led to a suspension from school. He was treated with dextroamphetamine with modest results. Psychological testing at age 8 showed marked reading delay; Justin had particular difficulty sounding out words. His handwriting was very poor. He began attending special education classes 2 hours a day. In the fifth grade, he exploded and threw a chair at a teacher, which led to a 5-day psychiatric hospitalization. An electroencephalogram (EEG) showed "right temporal slowing" but no actual seizure activity. He was started on carbamazepine in the hope this would reduce the aggressive outbursts. After 6 months of treatment, however, it was still unclear if the anticonvulsant was helpful and it was eventually discontinued. Justin barely passed the sixth grade. Repeat of psychological testing showed he was reading at the third-grade level. During the seventh grade, his aggressive outbursts increased, and he began making suicidal statements such as "How'd you feel if I wasn't around anymore?" He was caught with a small amount of marijuana in his school locker and was expelled. In the midst of an argument with his mother that night, he made a cut on his wrist and was hospitalized again. The managed care company approved a 3-day stay.

Justin was a patient of mine. By pure coincidence, I ran into Justin's father about seven years after this. The father reported that Justin had gone to residential treatment. There, he was diagnosed with bipolar disorder and tried on multiple medications, some of which clearly helped for at least a short time. When he turned 18, he left the residential center, began to use illegal drugs, and was arrested for burglary. He spent about a year in jail, then lived with various friends but kept in contact with his parents. While on probation, he found employment, stopped abusing drugs and drinking, and against all expectations he established a positive relationship with a woman whom he married. The marriage and his job remained stable, and he repaired his relations with

his parents. He has returned to community college part time, is now a parent himself, and currently shows no signs of bipolar disorder or antisocial personality.

How do we explain Justin's developmental course? Was he "misdiagnosed" as bipolar? Was comorbid conduct disorder the most accurate diagnosis all along? If so, what accounts for the remission of these symptoms with age? Did the aggressive intervention with residential treatment and psychotropic medication alter his long-term course? Cases like Justin's give us hope that while current research does not have all the answers, careful integration of findings from the literature and clinical experience can map the way to effective intervention. The previous work of my colleagues and I (Pliszka et al., 1999) was an in-depth scientific review of the topic of ADHD with comorbid disorders. This book takes a more clinical approach. While it is informed by the significant advances in the study of comorbidity of mental disorders with ADHD over the last decade, the study of each condition in the subsequent chapters revolves around a series of case studies. The goal here is to inform the practicing clinician of the variety of both pharmacological and psychosocial interventions that can be brought to bear in these difficult situations. While I have been involved in clinical and neuroimaging research in the last 20 years, I have spent half my time involved in the care of patients in a variety of settings ranging from a "private practice" university clinic to residential treatment centers. Moreover, the data from literally thousands of these patients has been consistently entered into a computer database that allows accurate documentation of the patients' clinical course. As Yogi Berra allegedly said, "You can observe a lot by just looking." This database contains a rich source of cases of children and adolescents with ADHD who also have conduct problems, affective and anxiety disorders, autism spectrum disorders (ASD), and substance abuse issues, among other serious complications. We mine this database to explore the management of very complex cases.

Defining Comorbidity

Comorbidity can be simply defined as two or more diseases occurring in the same individual. Angold, Costello, and Erkanli (1999) discussed several factors that influence this definition, and their framework is useful for developing the questions that we address in this book.

Disorder versus Disease

In general medicine, the pathophysiologies of many diseases are at present much better understood than in mental health. When we speak of the comorbidity of lung cancer and emphysema, each individual disease is a clearly separate clinical entity with a specific clinical course and treatment. Our knowledge of their pathophysiology allows us to understand that smoking is a major etiological agent for both. In mental health, we define *disorders* as "behavioral and psychological syndromes that deviate from some standard of normality" (Angold et al., 1999, p. 58). We do not know for certain if separation anxiety and generalized anxiety disorder (GAD) are truly different diseases or whether they are one disease with varied presentations at different developmental levels. If they are one disease there is no "comorbidity"; rather the problem is with our classification system. Similar issues will complicate our discussion of ADHD and comor-

bid bipolar disorder (BP)—particularly in distinguishing severe mood lability/aggression from manic cycling. Of course, clinicians cannot wait for nomenclature debates to resolve themselves in the DSM-V (or VI or VII!) before making a diagnosis for the patient who is in the office today.

Primary versus Secondary Disorders

Patients with diabetes frequently have impaired eyesight as they age; so one might say that blindness is often comorbid with diabetes. Diabetes can also lead to atherosclerosis in small blood vessels (microaneurysms), which in turn leads to hemorrhages in the retina. Through our knowledge of the pathophysiology of the disease, it is clear that the impaired vision is secondary to the diabetes (diabetic retinopathy). Again, we have no such detailed knowledge in psychiatry to make such a determination when two mental disorders coexist in a patient. When treating a child with comorbid ADHD and oppositional defiant disorder (ODD), clinicians often observe that the defiance and argumentativeness frequently resolve after medication treatment of the ADHD (Newcorn, Spencer, Biederman, Milton, & Michelson, 2005; Spencer et al., 2006). Does this mean that the ODD is "secondary" to the ADHD? In contrast, in children with ADHD and bipolar disorder, the onset of ADHD usually precedes the onset of mood symptoms by several years, and clinical experience is that treatment of ADHD does not improve the mood symptoms per se. Few would argue that bipolar is "secondary" to ADHD simply because it occurred later in the child's clinical course. Despite our imprecision in these matters, a critical clinical decision point is whether or not to regard a comorbid disorder as secondary to ADHD. Declaring comorbid disorder truly secondary to ADHD suggests that treatment of the ADHD should occur first. We examine a variety of cases where this approach is either warranted or contraindicated.

Developmental Comorbidity

When we say that two disorders are present *at the same time* in a patient, what time frame are we referring to? Do we mean at the exact moment a patient is in the clinic? Or do we mean the last week, month, or 6 months? Or perhaps even the child's entire lifetime? Angold et al. (1999) use the terms "concurrent" and "successive" comorbidity to refer to two different clinical situations: in concurrent comorbidity the child clearly meets criteria for two or more disorders at the present time (i.e., at the visit, has 8/9 inattention symptoms of ADHD and 6/9 symptoms of ODD), while successive comorbidity refers to a child who meets criteria for ADHD at one point in his or her life and, while the ADHD symptoms resolve with age, develops a new disorder such as dysthymia. In this latter case, has the ADHD "morphed" into depression or has it gone "underground"? Will the ADHD reemerge once the depression is treated? Or has the ADHD truly resolved such that the clinician is seeing the emergence of an unrelated condition?

Familial Comorbidity

The substantial role of genetics in the etiology of ADHD is now well established. Family studies consistently have shown that if a child has ADHD, 10–35% of first-degree relatives are likely to have the disorder as well (Biederman et al., 1992). If a parent has

ADHD, the risk of the child developing ADHD is as high as 57% (Biederman et al., 1995b). In adoptive children who were hyperactive, higher rates of hyperactivity were found in their biological parents relative to their adoptive parents (Cantwell, 1972; Morrison, 1980; Morrison & Stewart, 1971). Sprich, Biederman, Crawford, Mundy, and Faraone (2000) examined the rates of ADHD in the relatives of both adopted (i.e., nonbiological) and nonadopted children with ADHD. The rate of ADHD in biological relatives of children with ADHD was 18% compared to only 6% in the adopted relatives, suggesting a strong genetic effect. Twin studies compare conductance rates for ADHD in monozygotic and dizygotic twins to determine the relative influence of genes and environment on the variance in the symptoms of ADHD. Reviews of these studies consistently show that about 75% of the variance in ADHD traits is attributable to genetics (Faraone et al., 2005).

Angold et al. (1999) point out that comorbidity also is influenced by genetics. Relatives of children with ADHD have not only elevated rates of ADHD but higher than expected rates of antisocial personality, alcoholism, and substance abuse. It is also noteworthy that sometimes comorbidity will "breed true." For instance, children with ADHD alone do not have elevated rates of comorbidity of conduct disorder (CD) in their relatives, while children with comorbid ADHD/CD do. Moreover, the ADHD and CD "cosegregate," that is, the relatives of the child with ADHD/CD also tend to have *both* ADHD and antisocial behavior, suggesting that ADHD/CD is a separate genetic subtype from ADHD alone (Biederman et al., 1992). Similarly, while parents with depression have higher than expected rates of depression among their children, children of depressed parents also have higher rates of a range of disruptive behavior disorders (Angold et al., 1999). Family history, therefore, plays a role in helping us untangle comorbidity in the child. Yet, we must not "jump the gun." A parent with bipolar disorder may bring his or her child for treatment of defiance and argumentativeness, but we would not conclude the child has bipolar disorder based only on the parent history. Nonetheless, how should the parent's history inform treatment?

When Does Comorbidity Matter?

If a child with ADHD presents to your office with a runny nose, the child can be said to have ADHD with a comorbid rhinitis. For the mental health professional, it is difficult to think of any long-term consequence of such "comorbidity." We must have a set of rules for determining when a comorbid disorder really has clinical significance in the management of the patient. Otherwise we run the risk of concluding that everything is comorbid with ADHD, as every disorder in the DSM and every known disease has occurred in people with ADHD at one time or another. Fortunately, Jensen, Martin, and Cantwell (1997) have developed such rules for determining if a comorbid disorder (CM) associated with ADHD is clinically relevant.

Distinctive Clinical Picture

Children with ADHD/CM should differ in substantial ways from children with ADHD on measures other than the diagnostic criteria themselves. For instance, children with ADHD and social phobia should be seen as withdrawing from social interactions on the

playground by observers blind to the child's diagnostic status. If children with ADHD with and without a comorbid diagnosis differ only on the clinician's interview, without any "real-world" differences on behavior rating scales, peer interactions, educational achievement, and so forth, then the validity of the distinction is questionable.

Distinctive Demographic Factors

The ADHD/CM group may differ from the children with ADHD alone in terms of sex, ethnicity, or social class.

Differences in Psychosocial Factors

The ADHD/CM group may have a differential exposure to major societal stressors such as poverty, crime, urban decay, or exposure to violence.

Differences in Biological Factors

Are there differences between the ADHD/CM and ADHD groups in terms of genetic markers, brain anatomy, neuroimaging, or physiology? This approach is still in its infancy but holds great promise for the future.

Distinctive Family Genetic Factors

Does the ADHD/CM condition "breed true"? That is, if a child has ADHD/CM, is there an increased prevalence of both ADHD and CM in his or her relatives? Furthermore, do the ADHD and CM almost always occur in the same relative or does the child have some relatives with CM and others with ADHD? In the former situation, the case for ADHD/CM being a distinct genetic subtype is strengthened. In the latter case, the child most likely inherited two independent disorders from separate relatives and ADHD/CM is not distinct.

Distinctive Family Environmental Factors

Has the child with ADHD/CM been exposed to certain family experiences not shared by the child with ADHD alone? Have children with ADHD and anxiety disorders experienced more divorce or separation than those with ADHD alone? Are children with ADHD and CD more likely to have been exposed to domestic violence?

Distinctive Clinical Course and Outcome

Are children with ADHD with and without comorbid disorders different at follow-up? Do children with ADHD/CD have more criminal convictions? Do children with ADHD and depression have a higher rate of adult affective disorder than nondepressed children with ADHD? Are there differences in the life course of the ADHD itself for comorbid and noncomorbid children? Does the presence of the comorbid disorder make continuation of ADHD into adulthood more or less likely?

Unique Response to Specific Treatments

Do children with ADHD with and without comorbid disorders differ in their response to either psychopharmacological or psychosocial interventions?

In the subsequent chapters, we pay particularly close attention to each of these factors as we look at the different comorbidities.

Comorbidity in the Community and the Clinic

Epidemiologists and clinicians look at the world quite differently. The epidemiologist wishes to establish the true prevalence and incidence in a population. While clinicians tend to use these terms interchangeably, they are quite different (see Box 1.1), and it is prevalence that is most important to the study of comorbidity. Epidemiologists do not

BOX 1.1. Defining Prevalence and Incidence

Prevalence—defined as the total number of cases of the disease in the population at a given time, or the total number of cases in the population, divided by the number of individuals in the population. It is presented as a percentage. For instance, the prevalence of ADHD was found to be 8.7% by the U.S. National Health and Nutrition Survey for the period 2001–2004 (Froehlich et al., 2007). Prevalence is subtyped into:

- *Point prevalence*—a measure of the proportion of people in a population who have a disease or condition at a particular time, such as a particular date. It is like a snapshot of the disease in time.
- *Period prevalence*—a measure of the proportion of people in a population who have a disease or condition over a specific period of time (last month, last year).
- *Lifetime prevalence*—the number of individuals in a statistical population that at some point in their lives (up to the time of assessment) have experienced a "case" (e.g., a disorder), compared to the total number of individuals. (It is expressed as a ratio or percentage.)

Incidence—the number of new cases of a disease during a given time interval, usually 1 year. It can be expressed as a proportion or as a rate.

- *Incidence proportion* (also known as *risk*)—the number of new cases divided by the size of the population at risk. For example, if a stable population contains 1,000 persons and 43 develop a condition over 2 years of observation, the incidence proportion is 43 cases per 1,000 persons.
- *Incidence rate*—the number of new cases per unit of person-time at risk. In the same example as above, the incidence rate is 21.5 cases per 1,000 person-years, because the incidence proportion (43 per 1,000) is divided by the number of years of the study (2). *Incidence* is sometimes used alone as a shorthand for *incidence rate,* though this should be avoided.

look at clinical samples, but rather at samples of hundreds or thousands of children drawn from the community. If we take the prevalence of ADHD to ~7%, we then look at the prevalence of another disorder of interest (e.g., ODD/CD) in the general population and find that in a particular study, it is 8.0%. By chance alone, we would expect 8% of the children with ADHD to have comorbid ODD/CD. If this were the case, then the odds ratio of having ODD if the child has ADHD would be 1.0 (i.e., not different from chance). Suppose the prevalence of ODD/CD in the ADHD sample is 16%; then the odds ratio would be 2.0 (i.e., double the rate). Figure 1.1 resulted from a meta-analysis of 21 epidemiological studies of mental disorders in children. As can be seen, relative to the general population, patients with ADHD had greater than expected prevalence of ODD/CD (10 times), depression (5.5 times), and anxiety (3 times). These epidemiological studies are critical in showing us that comorbidity is not simply an artifact of children with more severe conditions being referred for treatment (i.e., referral bias).

These epidemiological studies can inform us about the comorbidity of common conditions such as depression, ODD, and ADHD. They are less well suited for the study of more rare conditions such as bipolar or tic disorders. For instance, only 6 of 1,420 (0.42%) children in the Great Smokey Mountain Study had a manic or hypomanic episode during the 3 months preceding the interview (Costello et al., 1996). For the study of these conditions, we must rely on clinical samples. Here, I would like to make

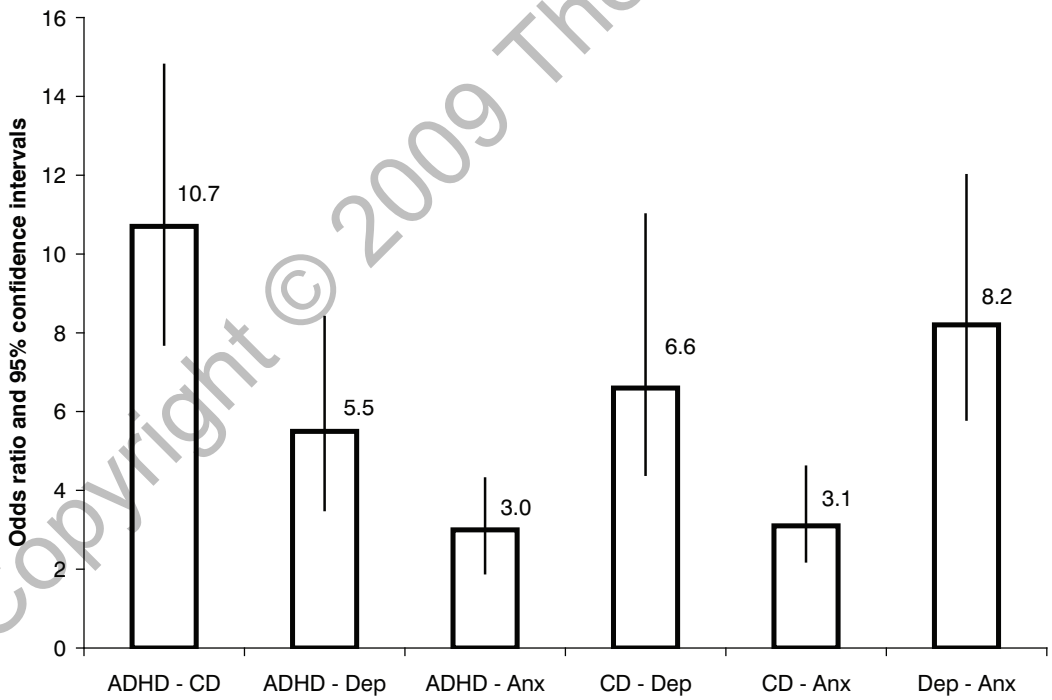

FIGURE 1.1. Risk of conduct, anxiety, and depressive disorders in children and adolescents with ADHD. From Angold, Costello, and Erkanli (1999). Copyright 1999 by Blackwell Publishing Ltd. Reprinted by permission.

an important point before presenting some prevalence data from my own practice—data from tertiary referral centers tell us what we are facing *in the clinic*. For instance, a child psychiatrist receiving referrals (as I do) of difficult-to-treat patients may see, in a given day, eight children with ADHD alone, six with ADHD and ODD/CD, and six with ADHD and bipolar disorder. This does not mean, however, that the prevalence of bipolar disorder in patients with ADHD in the community at large is 6/20, or 30%! So, I should not view the rates of bipolar disorder in my clinic as though they applied to the whole world. At the same time, I must deal with the reality that 30% of my patients with ADHD do have bipolar disorder, and I should not see the low rates of bipolar disorder in epidemiological samples as invalidating the reality I see in my clinic every day.

The Division of Child and Adolescent Psychiatry at the University of Texas Health Science Center at San Antonio is affiliated with several major clinical enterprises: (1) a "private practice University Clinic," (2) two private nonprofit child mental health clinics serving low-income children, and (3) two residential treatment centers for severely psychiatrically ill children (most of whom have suffered physical, sexual, or emotional abuse). One facility is for children of average IQ or above, the other treats children with mental retardation and/or ASD. For the last 5 years, data on these children's treatment have been systematically entered into our database. As one might imagine, the breadth and diversity of psychopathology in these children and adolescents is great, thus it is hoped that there is "something for everyone" in the data—regardless of discipline or practice setting.

These patients were not research subjects; all data were gathered as part of their routine clinical care (and deidentified for analysis here). Diagnoses were made according to the structured interview in Appendix Ib. This interview is not a fully validated structured research interview such as the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman et al., 1997) or the Diagnostic Interview Schedule for Children (DISC; Fisher et al., 1997; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). It was developed to train medical students and psychiatric residents to conduct their standard clinical interviews with children and their parents in a systematic fashion, but it has proven useful for all our faculty clinicians.

For the first broad look at the data, I extracted the diagnoses from all patients with ADHD who were active patients of any of the sites (defined as having had at least one visit in the last year); this yielded 1,035 patients for a snapshot of what is happening "right now" in the clinic. The comorbidity of these patients is shown in Table 1.1. The simplest way to look at comorbidity is to pair each comorbid disorder with ADHD. An inspection of this table shows how the San Antonio practice is atypical in some ways, yet is atypical in a fashion useful for the study of comorbidity. There are a substantial number of children (27%) with no comorbidity ("ADHD simplex"), though this number of patients with uncomplicated ADHD is clearly smaller than might be found in a primary care practice. Not surprisingly, ODD and CD are quite common (32% of the children with ADHD).

Comorbidity data are frequently displayed in research studies as in Table 1.1, yet reality is more complex, as shown in Figure 1.2. This Venn diagram illustrates that many children with ADHD have more than one comorbid disorder; in particular, there is a common phenomenon of "triple comorbidity" with ODD/CD. Of these patients with ADHD, 167 have an additional diagnosis of ODD/CD and nothing else (these

TABLE 1.1. Overall Comorbidity of Diagnoses among Patients with ADHD in a Medical School Setting

	San Antonio (n = 1035)		MTA study (n = 579)	
Diagnoses	Count	%	Count	%
No comorbidity	282	27.2		
ODD/CD	327	31.6	314	54.2
Intermittent explosive disorder	74	7.1		
Mood disorder not otherwise specified	90	8.7		
Depressive disorders[a]	109	10.5	22	3.8
Bipolar disorder (all subtypes)	121	11.7	13[c]	2.2
Anxiety disorders	149	14.4	194	33.5
Autism spectrum disorders[b]	50	4.8		
Psychotic disorder not otherwise specified	29	2.8		
Learning disabilities	101	9.8		
Tic disorder	17	1.6	63	10.9

[a]Includes major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified.
[b]Includes Asperger's disorder.
[c]Mania/hypomania.

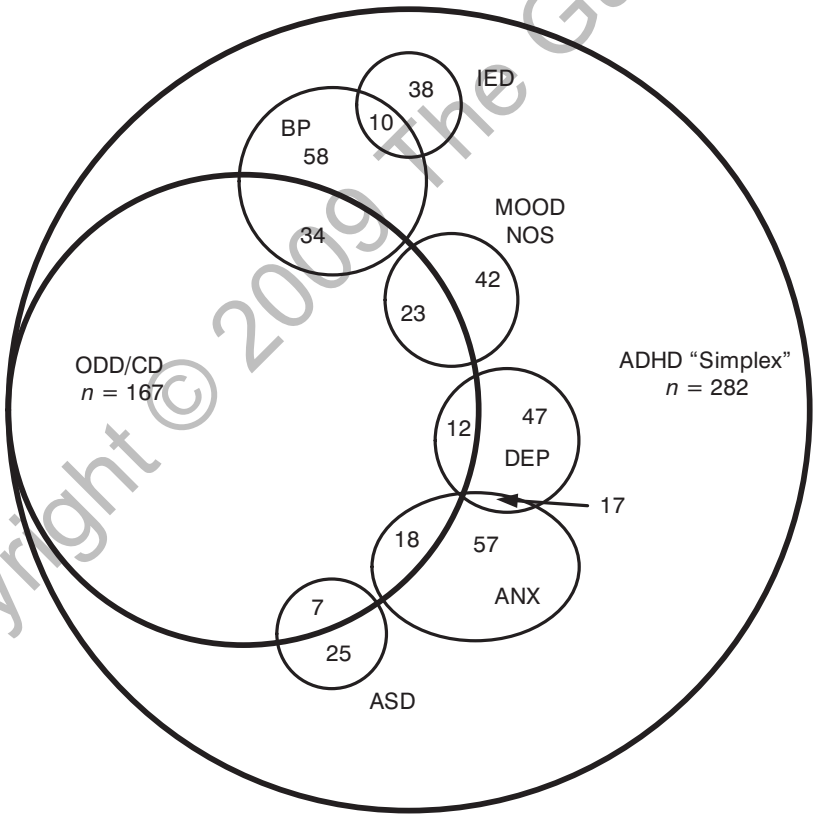

FIGURE 1.2. Overlap of diagnoses in children and adolescents with ADHD with more than one comorbid diagnosis.

patients are the focus of Chapter 2). Note, however, that when other major disorders are comorbid with ADHD, it is highly likely that ODD/CD is present as well. Note how ASD, anxiety, depression, nonspecific mood disorders, and BP tend to line up on the edge of the ODD/CD prevalence circle. This leads to one of the central arguments of this book—that argumentative, negativistic, and aggressive behaviors in children with ADHD are frequently (but not always) fueled by other comorbidities. The treatment of ADHD + ODD/CD and that of ADHD + ODD/CD combined with yet other comorbid disorders can be markedly different. This is a major focus of Chapter 2. In Chapters 5 and 6, we also examine two important but little researched phenomena. The diagnosis of mood disorder not otherwise specified was given to 8.7% of our ADHD population and these children are clearly separate from those with depression or bipolar disorder. What type of symptomatology leads to this diagnosis and how does it influence treatment? Note that 38 children were diagnosed with intermittent explosive disorder (IED) and no other disorder besides ADHD. Thus, clinicians separate out those with explosive aggression who do not have prominent mood symptoms. Is this a clinically relevant distinction? Chapter 3 will explore this issue. It is of interest to compare the rates of comorbidity in this database to that in the subjects of the National Institute of Mental Health Multimodal Treatment Study of ADHD (MTA; MTA Cooperative Group, 1999a, 1999b). The MTA study was designed to look at the treatment of ADHD per se, so major mental disorders such as bipolar disorder or ASD were excluded. Nonetheless, the comorbidity of ODD/CD was also highly prevalent in the MTA sample, as were depressive disorders. Despite the exclusion of children with BP, a small subgroup still met criteria for hypomania/mania. The difference in the rate of tic disorders between the two samples is harder to explain, but further illustrates the differences in comorbidity that can occur with different sampling strategies, even when focused on a clinical population.

There are also small groups of children with more than two comorbid diagnoses in addition to ADHD ("quadruple comorbidity"), as listed in Table 1.2. These children rarely find themselves in research projects (they meet exclusionary criteria), but they show up at the clinician's office and have stormy clinical courses. By looking in detail at these complex cases, we can have some approaches ready when these infrequent but serious situations arise.

Clinical Interview

Owing to its origins in psychoanalysis, the child mental health field has always emphasized the "open-ended" clinical interview, allowing both parent and child to state the reason for the visit and then to expand spontaneously, with the clinician following the interviewee's lead and in particular paying attention to his or her emotional state. Since the emergence of the successive versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) over the last several decades, mental health has moved to a more structured approach. Similarly, extensive interviews such as the DISC and K-SADS have been developed to make valid and reliable diagnoses in the research area. These research interviews can take several hours to administer and are rarely practical for use in the typical clinician's office. At the same time, when a child presents with multiple prob-

TABLE 1.2. "Quadruple Comorbidity" Children with ADHD Who Have More Than Two Comorbid Disorders

ODD/CD + mood disorder not otherwise specified + tic disorder	1
ODD/CD + mood disorder not otherwise specified + learning disabilities	4
ODD/CD + intermittent explosive disorder + mood disorder not otherwise specified	1
ODD/CD + intermittent explosive disorder + depression	1
ODD/CD + intermittent explosive disorder + BP + anxiety	1
ODD/CD + intermittent explosive disorder + anxiety	2
ODD/CD + depression + mood disorder not otherwise specified	1
ODD/CD + depression + BP	2
ODD/CD + depression + anxiety	7
ODD/CD + BP + anxiety	4
ODD/CD + BP + tic disorder	2
ODD/CD + BP + learning disabilities	2
ODD/CD + BP + anxiety + learning disabilities	1
ODD/CD + ASD + learning disabilities	1
ODD/CD + anxiety + tic disorder	1
ODD/CD + anxiety + learning disabilities	2
Intermittent explosive disorder + depression + BP	1
Depression + BP + anxiety	1
BP + ASD + tic disorder	1
BP + anxiety + ASD	4

lems, an open-ended approach can lead to confusion as the parent mixes the description of symptoms of ADHD, oppositional behavior, aggression, mood lability, anxiety and so on. The interview in Appendix Ib represents a compromise between the highly structured research interview and the very open-ended approach traditionally used by child mental health clinicians. This interview follows a number of basic principles:

The Interview Is Time Limited

It is designed such that information about even severely ill children can be obtained in 1 to 1½ hours, including interviews of both child and parent.

Preliminary Data Have Been Gathered

It is assumed that a demographic/developmental questionnaire and parent rating scales (see next section) have been obtained before the interaction with the parent. An example of the scale used in our clinic is in Appendix Ia. The questionnaire may either be mailed to the parent beforehand or the parent may arrive half an hour early to fill it out. The questionnaire should cover the child's medical history and developmental milestones. Ideally, a rating scale (particularly for ADHD symptoms) also has been obtained from the teacher. The interview format assumes that the clinician has had time to review these forms prior to meeting with the parent.

Both Parent and Child Will Be Interviewed

The degree to which the child provides key information for the diagnoses can be a contentious issue. With increasing demands on the time of mental health professionals, some clinicians have been interviewing only the parent, often with the child in the room. With the child present, however, the parent may not be frank in discussing many aspects of the history; furthermore the child may disrupt the interview. While interviewing *only* the parent alone may alleviate the problem with parental openness, not seeing the child might lead the clinician to miss internalizing symptoms (particularly suicidal ideation) as well as possible signs of abuse.

Interviewing both the parent and the child brings up the issue of integrating possibly incongruent data from both informants. What should the clinician do if the child states she is sad but the parent denied that the child was depressed? If the child denies any hyperactivity, should the clinician give this any weight? A long-standing clinical practice has emerged that adults (parents and teachers) are better reporters of children's disruptive behaviors whereas children themselves are more reliable when it comes to internalizing symptoms, such as depression or anxiety (Edelbrock, Costello, Dulcan, Conover, & Kalas, 1986; Loeber, Green, Lahey, & Stouthamer-Loeber, 1989; Reich & Earls, 1987; Welner, Reich, Herjanic, Jung, & Amado, 1987). Bird, Gould, and Staghezza (1992) performed DISC interviews on several hundred parent–child pairs. DISC diagnoses were generated, and then a clinician made a separate diagnosis of the child, which served as the external validating criterion (the "gold standard"). Statistical methods were used to determine if, for a given diagnosis, the parent or child data were most critical to make the diagnosis. For instance, if a child was given a diagnosis of ADHD by the clinician, did the parent or the child endorse the inattention and hyperactivity items on the DISC? Or did they both endorse symptoms of ADHD? For ADHD and ODD, *only* the parent DISC predicted the diagnoses, whereas for anxiety and depressive diagnoses, *both* the parent and child DISC contributed to the diagnosis.

The data of Bird et al. (1992) clearly showed that parents and children agree only about 20% of the time. Using the method of Loeber et al. (1989), they examined the percentage of time children endorsed a symptom if their parent had said the child had it. Of note, if the parent said the child fidgeted, about 45% of the children agreed that they fidgeted. If, however, the parent said the child failed to finish things, only 18% of the children agreed that they had this problem. A similar pattern was found for internalizing symptoms. If the parent stated the child worried a great deal, 58% of the children agreed. If the parent stated the child was depressed, only 20% of the children agreed. If a child says he or she has a symptom, what percent of parents agree? The pattern is not any more consistent. Bird et al. (1992) next looked at the prevalence of diagnoses in their sample if they based the diagnoses on the parent interview only, the child interview only, or a combination of the parent and child interview. In the latter method, if either the parent or the child DISC interview yielded a diagnosis, that diagnosis is regarded as present. Basically, the either–or method yields somewhat higher prevalence estimates of the disorders. Children will deny they have ADHD or ODD when adults clearly state it is present, but they will report more internalizing symptoms than adults have observed. As we explore each

major comorbid disorder in subsequent chapters, we discuss in more detail how to handle specific situations.

The Format for the Parent Is Structured

The interview assumes only a brief time for assessing the chief complaint before the clinician moves in to gather systematic information from the parent about each major DSM-IV childhood diagnostic criterion—I refer to this as "therapeutic interrupting." If the parent begins to move into an extensive discussion of how his or her divorce may be affecting the child, I say, "That is very important information and we will need to come back to it, but let me be sure that I have all the information about your child's symptoms." This allows me to launch into asking specific questions. Naturally, since we are dealing with ADHD with comorbid disorders, documenting the presence of ADHD and the most common comorbidities (ODD and CD) takes the stage first. The first page of the interview contains blanks to enter the result of whichever DSM-IV-based rating scale for ADHD, ODD, and CD the clinician has chosen (see Table 1.3), as well as a section for the clinician to use clinical judgment in interpreting the rating scale.

The interview for affective disorders focuses first on the child's *current* mood state and places heavy emphasis on quantifying the frequency and magnitude of abnormal mood states. The boxes on the form are only an endpoint—a series of clinical probes needs to be used to gather the data needed for differential diagnosis of an explosively aggressive, mood-labile child with ADHD. Is it intermittent explosive disorder, a manic or mixed episode of bipolar disorder, or a severe major depressive episode with psychomotor agitation? In the affective disorder chapters, we go into detail about such critical issues as how to distinguish irritable mania from irritable depression (or the irritability of ODD) and mixed states versus ultra-rapid cycling, and how to determine the time of onset of an abnormal mood state. Once the current mood state is established, the presence or absence of both neurovegetative signs and first-rank symptoms of mania should be determined.

It is then most logical to proceed to asking about past history of mood disorder, in particularly distinguishing between the child who has clear-cut episodes of depression or mania versus those who seem to have had a chronic course of abnormal mood. Issues including age of onset of mood disorder, chronicity, and phenomenology have been much debated in the literature (Biederman, 1998; Carlson, 2007; Klein, Pine, & Klein, 1998). They have also been much debated in the lay media since the emergence of data showing that the prevalence rate of visits to clinicians for bipolar disorder in children has grown from 25/100,000 in 1994–1995 to 1,003/100,000 in 2002–2003 (Moreno et al., 2007). Chapters 3 and 4 focus on this issue in detail.

The interview proceeds with questions that screen for the anxiety disorders, psychotic symptoms, and substance abuse issues. There are also screening questions for ASD, but the presence of these on this interview would only trigger further evaluation, not serve as a definitive diagnosis. As always, data about the child's past psychiatric treatment would need to be documented. (It is assumed that medical history is covered in the developmental questionnaire.)

The Format for the Child Is Unstructured, Combined with Self-Report Rating Scales

Most children (and many adolescents) would be bored repeating such a full format of structured questions, and given that children often add limited information to the diagnosis of ADHD/ODD/CD (Biederman et al., 2007b), the interview focuses instead on internalizing symptoms, where the child can give the clinician the greatest insight. After a period of establishing rapport, it is useful to get the child's sense of externalizing symptoms by asking, "Your parents have mentioned that you seem to have a lot of trouble paying attention, sitting still, or staying organized. What do you think about that?" The same can be done for the symptoms of ADHD or ODD/CD. It is generally a good sign if the child has insight into the presence of these problems, but his or her awareness of them is not necessary to confirm the diagnosis of an externalizing disorder, nor would the child's denial of them negate reports from teacher and parents. Fairly quickly, the clinician should move to exploring internalizing symptoms by saying, "I would like to ask some questions about your feelings." We administer self-report depression and anxiety scales (see below) and then use these scales to explore the problems related to these feelings. Specific questions are asked regarding substance abuse, suicidal thoughts and actions, and possible abuse. Finally, the child's current mental status is documented.

Rating Scales

Table 1.3 describes a variety of rating scales useful in the assessment of the child with ADHD and comorbidity. Since assessment of ADHD is always the starting point, a scale that covers all 18 of the DSM-IV-defined symptoms of ADHD is key; all of the scales also include well-validated ratings of ODD and CD. The clinician dealing with comorbidity should also gather information from the parent dealing with a broad range of symptoms. The table contains scales that explore depressive, manic, and anxiety symptoms. The Child Mania Rating Scale (CMRS; Pavuluri, Henry, Devineni, Carbray, & Birmaher, 2006b) has proven particularly helpful in conjunction with the clinical interview in the differential diagnoses of mood lability. Parent and teacher measures of aggression, independent of diagnosis, are also helpful as aggression is often a target symptom regardless of the type of comorbidity.

The child should fill out any self-report scales during the visit, either in the presence of the clinician or with a trained administrative staff in the office. Children should not fill out such scales at home or in the waiting room with the parent looking over their shoulder. Having the child fill out the questionnaire in the presence of the clinician allows him or her to follow up immediately on any statements that cause concern (such as items related to suicidality) as well as assess the validity of the child's responses.

We have used the Mood and Feelings Questionnaire (MFQ; Angold et al., 1995; Messer et al., 1995) and the Screen for Child Anxiety Related Emotional Disorders (SCARED; Birmaher et al., 1997) as our child self-report forms. They are straightforward scales, make clinical sense, and are available without charge. This does not detract from the other scales in the table—scales that are commercially available often have better and more up-to-date normative data; they are more likely to be available in computerized form.

TABLE 1.3. Common Behavior Rating Scales Used in the Assessment of ADHD and the Most Common Comorbid Disorders

Domain	Name of scale	Description and reference
ADHD	Academic Performance Rating Scale (APRS)	The APRS is a 19-item scale for determining a child's academic productivity and accuracy in grades 1–6. It has six scale points. Construct, concurrent, and discriminant validity data, as well as norms (n = 247), are available (Barkley, 1990).
ADHD	ADHD Rating Scale–IV	The ADHD Rating Scale–IV is an 18-item scale using DSM-IV criteria (DuPaul, Power, Anastopoulos, & Reid, 1998).
ADHD	Brown ADD Rating Scales for Children, Adolescents and Adults (BADDS)	Brown ADD Rating Scales consists of four separate scales with norms for preschoolers, children, adolescents, and adults and assess a wide range of symptoms of executive function impairments associated with ADHD/ADD. They contain items beyond the DSM-IV ADHD criteria which assess organization skills, regulating alertness, and managing frustrations and emotions as well as working memory (Brown, 2001).
Broad	Child Behavior Checklist (CBCL)	The CBCL is available in preschool and school age (6–18 years) forms, and each has about 100 items assessing a wide variety of problems in the areas of Aggressive Behavior; Anxious/Depressed; Attention Problems; Rule-Breaking Behavior; Social Problems; Somatic Complaints; Thought Problems; and Withdrawn/Depressed. The school-age form contains six DSM-oriented scales: Affective Problems, Anxiety Problems, Somatic Problems, Attention Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Conduct Problems. Scoring yields T scores (> 65 borderline, >70 is the clinical cutoff) for each scale as well as broad Externalizing and Internalizing symptoms.
ADHD	Conners 3	The parent form includes 110 items, the teacher form 115 items, and the self-report form 99 items. The short form, consisting of 43 items on the parent form, 39 on the teacher form, and 39 on the self-report form, can be used for screening. ADHD and Global Indexes are included. (Conners, 2008).
Broad	Home Situations Questionnaire—Revised (HSQ-R), School Situations Questionnaire—Revised (SSQ-R)	The HSQ-R (14 items) and the SSQ-R (8 items) are filled out by the caretaker and teacher, respectively (Barkley & Murphy, 2005). Each has the same structure: The informant responds "Yes" or "No" as to whether the child has problems in common situations (playing with other children, being in the car, individual desk work in class, recess). If the informant responds "Yes," they rate the severity of the problems on a scale from 1 (mild) to 9 (severe).
Broad	Swanson, Nolan, and Pelham (SNAP-IV) and SWANP	The SNAP-IV is a 26-item scale that contains DSM-IV criteria for ADHD and screens for other DSM diagnoses. The SWANP is a 30-item scale that measures impairment of functioning at home and at school (Swanson, 1992).
ADHD and ODD/CD	Vanderbilt ADHD Diagnostic Parent and Teacher Scales	Teachers rate 35 symptoms and 8 performance items measuring ADHD symptoms and common comorbid conditions (Wolraich et al., 2003a). The parent version contains all 18 ADHD symptoms with items assessing comorbid conditions and performance (Wolraich et al., 2003b).
Depression	Children's Depression Inventory (CDI)	The CDI is a 27-item scale. On each item, the child selects the option that best fits him or her—"I am sad all the time," "I am sad some of the time," "I am never sad." Not diagnostic, but useful in screening and documenting response to treatment (Kovacs, 1992).

(cont.)

TABLE 1.3. *(cont.)*

Domain	Name of scale	Description and reference
Depression	Mood and Feelings Questionnaire (MFQ)	The MFQ comprises parent and child self-report versions of a 37-item scale covering a wide range of depressive symptoms (Angold et al., 1995; Messer et al., 1995). No charge for use, but permission of author required (see *devepi.mc.duke.edu/MFQ.html*).
Mania	Child Mania Rating Scale—Parent Version (CMRS-P)	The CMRS-P is a mania rating scale designed to be completed by parents. It includes 21 items reflecting the DSM-IV criteria for a manic episode. Each item is answered on a 4-point Likert-type scale anchored by 0 (Never/Rare), 1 (Sometimes), 2 (Often), and 3 (Very Often) (Pavuluri et al., 2006b).
Anxiety	Revised Manifest Anxiety Scale (RCMAS)	The RCMAS has 37 items written at third-grade level. The child answers "Yes" or "No" to each item. Well-established norms, not diagnostic, but useful in screening and documenting response to treatment (Reynolds & Richmond, 1997).
Anxiety	Screen for Child Anxiety Related Emotional Disorders (SCARED)	The SCARED is a 38-item scale with parent and child forms. The subject responds to each item with 0—not true, 1—sometimes true, or 2—often true. Yields five factors: somatic/panic, general anxiety, separation anxiety, social phobia, and school phobia. Discriminates depressed/anxious children from those with disruptive behavior disorders. No norms as yet (Birmaher et al., 1997).
Anxiety	Multidimensional Anxiety Scale for Children (MASC)	The MASC is a 39-item scale with four factors: physical symptoms, social anxiety, separation anxiety, and harm avoidance. Fourth-grade reading level (March et al., 1997).
Aggression	Modified Overt Aggression Scale	This is a clinician-rated scale covering verbal and physical aggression against others, self, property, and animals (Coccaro, Harvey, Kupsaw-Lawrence, Herbert, & Bernstein, 1991).
Aggression	Overt Aggression Scale	This is a 20-item scale filled out by parent or teacher regarding the child's aggressive behavior toward others, self, or property in last week (Kronenberger, Giauque, & Dunn, 2007).
Aggression	Children's Aggression Scale	This scale includes parent and teacher ratings of specific aggressive acts (Halperin, McKay, Grayson, & Newcorn, 2003; Halperin, McKay, & Newcorn, 2002).

Dual versus Differential Diagnosis

The clinician must have an algorithm in his or her head for classifying the many symptoms encountered in the psychiatric interview, as well as knowing how to sort them into diagnostic categories. A case example (Pliszka et al., 1999) is helpful in illustrating this process:

Nine-year-old James was brought to the clinic by his mother because of poor school performance. Currently a third grader, he had been described by his teachers throughout elementary school as careless, sloppy, and unable to finish his work. He fidgets and makes noises but does not get out of his seat or run around the classroom. On the playground, he is shy and does not play with the other children. The teacher reported that he has said, "I'm ugly and stupid," when asked why he does not get along with the other children.

The mother also has trouble getting James to complete tasks at home. He seems unable to concentrate on his homework. He throws temper tantrums when pushed to do things. He cries, stamps his feet, and throws things. He does not become physically aggressive. He often says, "I hate you" or "I hate my life" when very angry. He does not want to go to bed at night and calls out for water and says he can't sleep. Once asleep, he stays asleep through the night. He has always been a picky eater. He is very nervous in new situations. He has never tried to deliberately hurt himself. His mother states that James is in a "bad mood" much of the time, but does not say he is sad.

During the examination, James is cooperative and friendly. He doesn't seem restless during the interview, but it is difficult to get James to concentrate on the questions asked. He says he hates school because "it is boring and the kids are mean." He states he is sad because there is no one to play with in his neighborhood and his dad does not always visit him. He is scared of the dark and worries that something bad will happen to his mom. He once wished he was dead when his mom grounded him but denies any suicidal ideation currently.

This case presents with a mixture of anxiety, depressive, and inattentive/hyperactive symptoms. The clinician must determine whether this is a case of ADHD, depression, or a truly comorbid case of ADHD and depression. Figure 1.3 illustrates how a clinician can step through the data to arrive at the appropriate conclusion. After a structured interview, one of several patterns may be evident. James may meet full criteria for ADHD, with onset of the symptoms before age 7. The interviewer detects symptoms of depression, but the child does not meet the full criteria for major depressive disorder (MDD) or dysthymia. The depressive symptoms may stem from a variety of issues. They may be centered on the child's unhappiness over the consequences of his ADHD behavior. Children will not play with him because he acts silly or is irritating. He might miss activities because of frequent misbehavior. It does not constitute a true depressive disorder, though it certainly may be the focus of psychosocial intervention. The psychotropic management would focus on the ADHD, most likely beginning with stimulant treatment. Antidepressant medication would not be the first-line treatment in such a child. The primary diagnosis made would be ADHD, though a diagnosis of adjustment disorder with depressed mood might be entertained if the demoralization symptoms were significantly impairing. The child would not be regarded as truly comorbid.

In the middle box of the chart, a somewhat more complex outcome of the interview is illustrated. The child clearly meets full criteria for MDD, and the child reports pervasively depressed mood. ADHD symptoms are present, but the child does not meet the full criteria for ADHD. He has a number of inattentive symptoms, as well as three impulsive–hyperactive symptoms. Age of onset is a critical issue. If these symptoms were not present before age 7, by definition he does not have ADHD. Equally important is whether these ADHD symptoms had their onset only after the depressive symptoms emerged. If so, it is likely they may be secondary to the MDD. The depression would be the focus of the psychotropic management, as well as any psychological intervention. It would be expected that the inattentive and impulsive symptoms would resolve once the child's depression lifted. Again, this would not be a truly comorbid case.

The box to the far right of Figure 1.3 illustrates the most complex situation of all. After the interview, the child is found to fully meet criteria for both disorders. The child is inattentive, impulsive, and hyperactive; these symptoms are pervasive and have

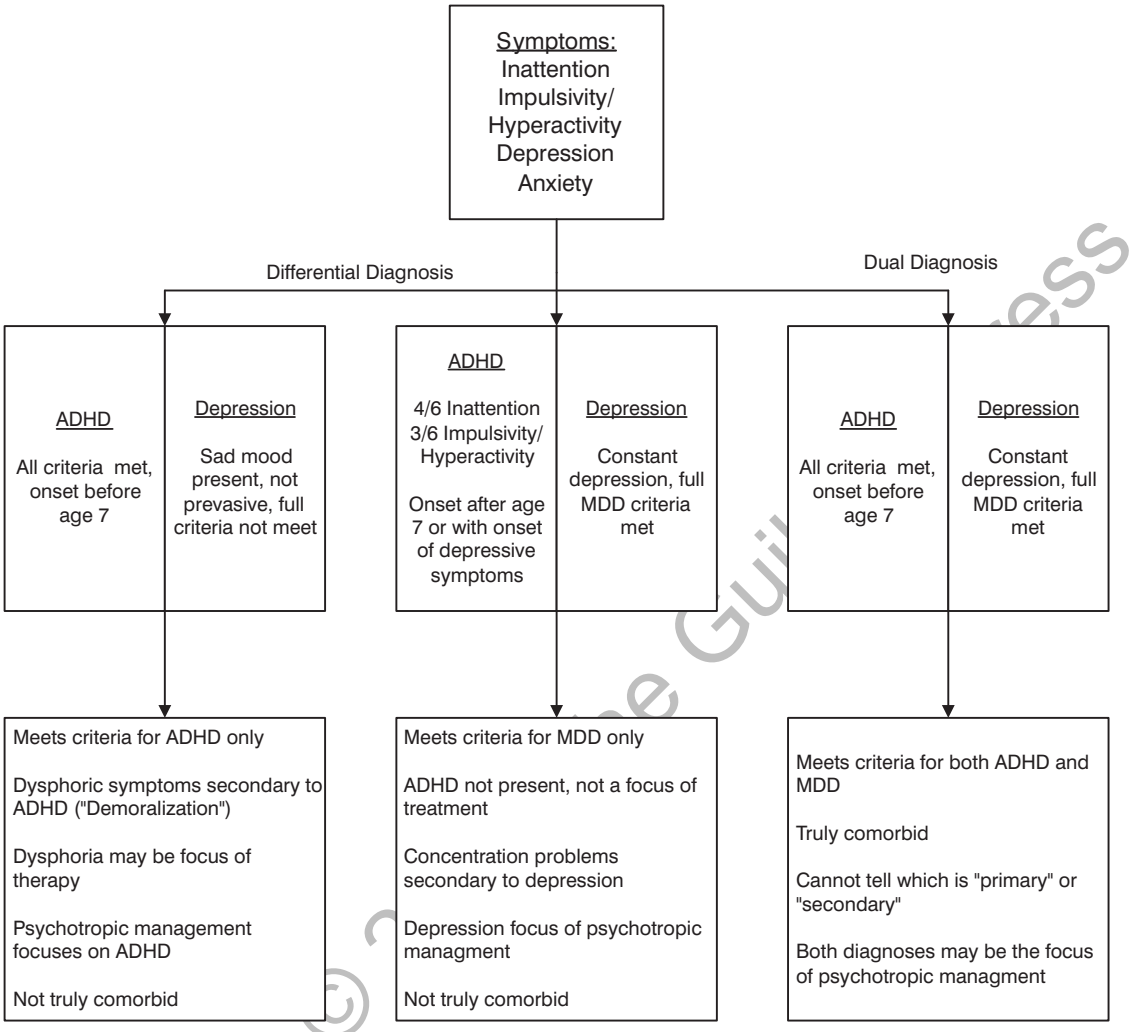

FIGURE 1.3. Differential versus dual diagnosis in the evaluation of comorbid disorders in ADHD.

been present since early childhood. The child is also pervasively depressed, and has multiple neurovegetative signs. This is a truly comorbid case. There is no way to tell for sure which diagnosis is "primary" or "secondary." Indeed, the child may be suffering from two independent disorders, each requiring its own treatment. Thus both diagnoses may be the focus of psychotropic or psychological treatment.

Treatment Issues in Comorbidity

Treatment of ADHD with comorbid disorders involves a multifaceted, multidisciplinary approach, with both pharmacological and psychosocial treatment (primarily behavior therapy) playing central roles. Appendix II provides a review of the major pharmaco-

logical agents used in the treatment of ADHD, affective and anxiety disorders, psychosis, tics, and aggression. This information is concentrated in one place so that it will not be necessary to repeat details about dosing, side effects, and monitoring in each chapter, particularly as some agents (such as atypical antipsychotics and antidepressants) can be used for a variety of conditions. In the chapters themselves, the focus will be on the combination of agents used to treat both ADHD and the comorbid condition. Here there is limited research data to guide us, but the database should provide a wealth of case examples.

It is not the intent of this book to provide a detailed instruction manual on behavior or other forms of psychotherapy. The original work of my colleagues and I (Pliszka et al., 1999) contains an excellent overview of the principles of behavior therapy; there are also many textbooks on this topic (Barkley, 1997b; Barkley, 2006a; McMahon, Wells, & Kotler, 2006; Smith, Barkley, & Shapiro, 2006). For the treatment of severe oppositional and aggressive behaviors, we examine a number of social, cognitive, and collaborative approaches that show promise in this population (Greene & Ablon, 2006; Larson & Lochman, 2002). As we move toward the internalizing disorders, the focus will shift to when cognitive therapy is appropriate. Again, there is rich literature on this topic regarding the treatment of both depressive and anxiety disorders with this technique (Reinecke, Dattillio, & Freeman, 2006). The case examples focus on the implementation of these therapies in unique or difficult situations. The MTA is a valuable source of information on how comorbid disorders affect the clinical course of ADHD. Because we refer to this study so often, an overview of its many findings is in order.

The MTA Study

The MTA is one of the few long-term studies of treatment outcomes for ADHD. Subjects underwent a year of active treatment (MTA Cooperative Group, 1999a, 1999b), then had follow-up assessments 2 years (MTA Cooperative Group, 2004a, 2004b), 3 years (Jensen et al., 2007a; Molina et al., 2007; Swanson et al., 2007a, 2007b), and most recently 6–8 years (Arnold & Molina, 2007; Elliott & Swanson, 2007; Molina, 2007) after the formal research treatment ended. Subjects will most likely be followed into adulthood. A large number of children with ADHD ages 7–10 years ($n = 579$) were randomized to one of four groups for 13 months of active intervention:

1. Medication management (Med-Mgt), wherein children first underwent a 28-day double-blind placebo-controlled methylphenidate trial to determine the best dose of stimulant for symptom reduction and then received 13 months of regular medication follow-up. Pharmacotherapists had regular access to parent and teacher behavior rating scales.
2. Intensive behavior therapy (Beh), consisting of 35 parent training sessions, biweekly consultation with the child's teacher, an 8-week summer camp program designed for children with ADHD, and 3 months of classroom aide support.
3. Combined treatment (Comb), consisting of Med-Mgt and Beh together.
4. Community comparison (CC).

It would not be ethical to deprive children with ADHD of all treatments for a year, so the control group was referred for standard treatment in the community. About two-thirds of these children received medication treatment, primarily with stimulants.

Among the many strengths of the MTA were the large sample, the high degree of comorbidity (see Table 1.1), the fact that girls made up 25% of the sample, and the significant number of Hispanics and African Americans included. The MTA findings address several major areas: (1) how comorbidity affects symptoms at entry to the study, (2) outcome of acute treatment at the end of the year, and (3) outcome at future time points *after active treatment had ended*. This latter point is particularly important in understanding the results of the MTA. After the first year of the study families chose whichever standard treatment they wished, or they could drop out of treatment. Children who were in the behavior group could go on medication, while children in the medication group could stop medication. For the purposes of the analyses in years 2, 3, and 6–8, children were still classified according to the group in which they were originally randomized.

Figure 1.4 is the now famous figure showing how the children undergoing different treatments in the first year of the MTA fared over time. All of the children met DSM-IV criteria at study entry; at 14 months all four groups showed improvement in symptoms such that many children no longer officially met criteria for ADHD (MTA Cooperative Group, 1999a). As shown, the two groups that were treated with rigorous medication management were significantly better than the CC and Beh groups, which were not different from each other. Beh appeared to do as well as the "standard" CC group in reducing symptoms, so it might be claimed that behavior therapy works as well as medication and is an alternative to medication. However, when children who had not received any medication were excluded from the CC group, the CC group in fact did better than the Beh group. Thus, behavior therapy is not as effective as medi-

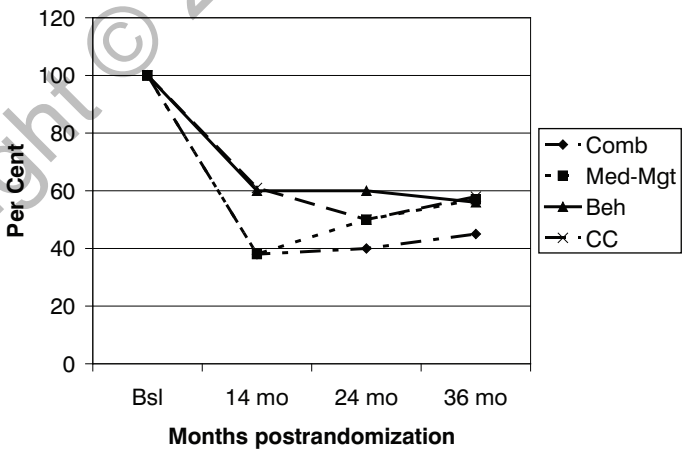

FIGURE 1.4. The long-term outcome of children with ADHD in the Med-Mgt, Beh, Comb, and CC groups of the MTA study. From Jensen et al. (2007a). Copyright 2007 by Wolters Kluwer. Reprinted by permission.

cation treatment. The American Academy of Child and Adolescent Psychiatry (2007) practice parameters regard pharmacological intervention as the first-line treatment for ADHD.

Before moving to the long-term outcome, it is critical to look at moderators that affected the response of subgroups in the sample. Not surprisingly, comorbidity was a key factor, as shown in Figure 1.5 (Jensen et al., 2001; MTA Cooperative Group, 1999b). The *y*-axis represents effect size (see Box 1.2 for a discussion of effect sizes) over CC, that is, how much greater the effect of the structured treatment was over CC. Note that for children with ADHD alone, Beh did not have any effect greater than CC (effect size = 0), whereas there was a significantly larger effect size for Med-Mgt and Comb over CC (though not different from each other). The comorbidity of ODD/CD did not moderate treatment—the lines for ADHD plus ODD/CD essentially overlap with the ADHD group. This means that the children with comorbid ODD/CD responded to treatment just like the ADHD group. The pattern was quite different for comorbid anxiety, however. Note that children with comorbid anxiety were much more responsive to all treatments, with a large effect size compared with the CC group. Comb was more effective than Med-Mgt. This was particularly true for the group with dual comorbidity, that is, children with ADHD, ODD/CD, *and* anxiety. Hinshaw (2007) described other moderators of outcome in the MTA. Children on public assistance and African American children responded better to Comb treatment. In contrast, children with depressed parents and those with more severe ADHD or low IQ showed worse response to both Med-Mgt and Comb. As Hinshaw (2007) points out, "these results are sobering, as they reveal a relative failure of the intensive MTA treatment algorithms to help those children in the study who were most in need of intervention" (p. 96).

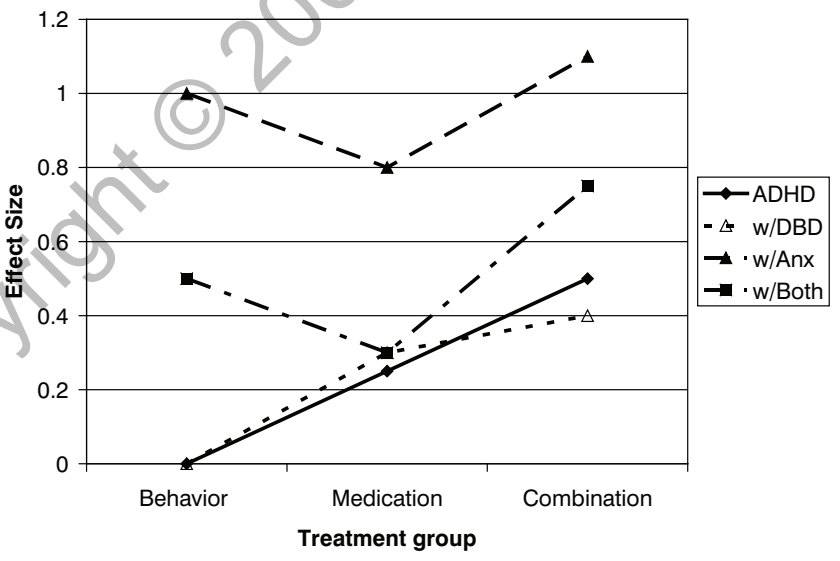

FIGURE 1.5. Effect of comorbidity on treatment outcome in the MTA study. From Jensen et al. (2001). Copyright 2001 by Wolters Kluwer. Reprinted by permission.

BOX 1.2. Effect Size for Clinicians

The concept of effect size is important because it has become a common way to present results from treatment studies. It gets beyond statistical significance and helps tell us when a treatment is clinically significant. The effect size of a treatment is calculated from the simple equation below:

$$\frac{\text{Mean } RX_1 - \text{Mean } RX_2}{\text{Standard Deviation}}$$

The two treatments may be an active treatment and a placebo, or two different active treatments. The effect size is unitless because the values of the outcome measures (laboratory value, rating scale scores, etc.) appear in both the numerator and denominator. Thus, effect sizes can be used to compare results from studies using different measures. To use a stimulant trial as an example, suppose two groups of children with ADHD are randomized to placebo or drug and a rating scale is obtained after 2 weeks of treatment. Assume the mean of the placebo group is 2.1 and the stimulant group is 1.0, with a standard deviation of 0.8. The effect size is calculated as 1.4. Contrast this with an antidepressant trial that uses a depression rating scale as an outcome variable. The active drug group has a mean of 52, while the placebo group has a mean of 64, with a standard deviation of 35. The effect size is 0.46. Thus, effect sizes range between 0 and 2.0, though in clinical practice they are rarely above 1.0. The stimulant effect size is "large," indicating that it is observable by the family and clinician, so a relatively small sample will be required to show statistical significance. In contrast, the effect size for the antidepressant is moderate, and a much larger sample is required for that difference in the means to be significant. It also means the effect will not be as strongly noticed at the level of the individual patient. Effect sizes of 0.2–0.3 are less likely to be clinically significant, as they would only become statistically significant with very large samples. Many public health practices (e.g., eating low-fat foods) have very small effect sizes, but they have great public health significance if millions of people can be induced to adopt them.

Once active treatment stopped, the four groups converged, and many children returned to active ADHD diagnostic status at 24 months (MTA Cooperative Group, 2004a) (again, see Figure 1.4). The Med-Mgt group continued to show significant superiority over the Beh and CC groups for ADHD and ODD symptoms at 24 months, although not as great as at 14 months. Additional benefits of Comb over Med-Mgt and of Beh over CC were not found. By 36 months, however, there were no differences at all between the groups in ADHD status. All four groups remained improved over their baseline status, and 40% of the children no longer met criteria for ADHD even though many were not on medication (Jensen et al., 2007a). At 36 months, 70% of the Med-Mgt and Comb groups were still taking medication, compared with 60% of the CC group and 45% of the Beh group. While there were differences in outcome between those taking and not taking medication at 24 months, there was no such difference at 36 months (Swanson et al., 2007b)! These findings were not any different at the 6- to 8-year follow-up. All four groups showed declines in impulsivity–hyperactivity (though still more impaired than controls), and they were not different from each other in clini-

cally meaningful ways (Arnold et al., 2007). Is it possible that taking medication for ADHD really makes no difference in the long run?

Looking at data in a naturalistic outcome study is very complex. One possibility is that only the most severely ill children stayed on medication, thus masking the beneficial effect of the treatment. How could this happen? Imagine a group of 200 children with ADHD, half very severely impaired, the other half only mildly impaired. All are treated with medication. Over time, the mildly impaired group ends up with 20 on medication and 80 off medication (because the less severe children "grew out" of their ADHD). In contrast, 80 of the severely ill group are on medication, and only 20 are off medication. Assume we are using a scale like the SNAP (Swanson, Nolan, and Pelham Questionnaire) with a 0–3 range. The 80 severely ill children on medication have a SNAP of 2.0, while the 20 off medication have a SNAP of 2.5. The mildly ill children on medication have a SNAP of 1.0; the mildly ill children off medication have a SNAP of 1.5. Thus both groups show a beneficial effect of medication, but when you average the two groups together to compare all subjects on and off medication, both groups have a mean SNAP of about 1.8. Swanson and colleagues (2007b) performed a "propensity score" analysis to rule out this possibility. They *did not* find the above scenario. They divided the MTA sample into five quintiles based on severity of symptoms and did find that those with greater severity were more likely to take medication, but being on or off medication did not affect outcome within any given quintile. So what is going on?

First, none of the 36-month data take away from the fact that medication showed strong effects in the 14- and 24-month follow-up, superior to the only alternative to medication, that is, behavior therapy. Behavior therapy also showed no effect in the 36-month data. Most likely, there are biological changes in the subjects that are not related to initial severity. Thus, some children with ADHD do have improvement in their symptoms that is likely based on brain maturation (Shaw et al., 2007); these children no longer need medication. Others have deterioration (perhaps based on development of comorbidities) that leads to poor outcome in spite of being on medication. What is needed to really resolve the issue is a long-term (5–10 years) *controlled* trial of medication, as difficult as this might be. An analogy to the long-term treatment of asthma might be helpful. As asthmatic children mature, some outgrow their asthma while others go on to develop serious airway problems. Inhalers improve breathing during an asthma attack, but if we followed up these asthmatic children into adolescence we might also find that inhaler use was unrelated to outcome. Yet, no one would suggest not using inhalers during acute asthmatic attacks.

We will have much more to say about the MTA in subsequent chapters. Let us close our discussion of the MTA with a final, important graph (Figure 1.6) examining outcome for the children (Swanson et al., 2007b). Using a specialized statistical technique, it was shown that the children with ADHD fell into three classes: (1) those who showed gradual improvement over time (34% of the sample), (2) those who showed immediate strong improvement and maintained it (52%), and (3) those who showed initial gains but then deteriorated over time such that by year three they were as impaired as at baseline (14%). None of the classes were in remission; all remained more impaired than a normative control group. Class 2 was less impaired at baseline. But, classes 1 and 3 were similar in baseline impairments, despite their very different patterns of outcome, again showing that baseline severity is not the only factor influencing outcome.

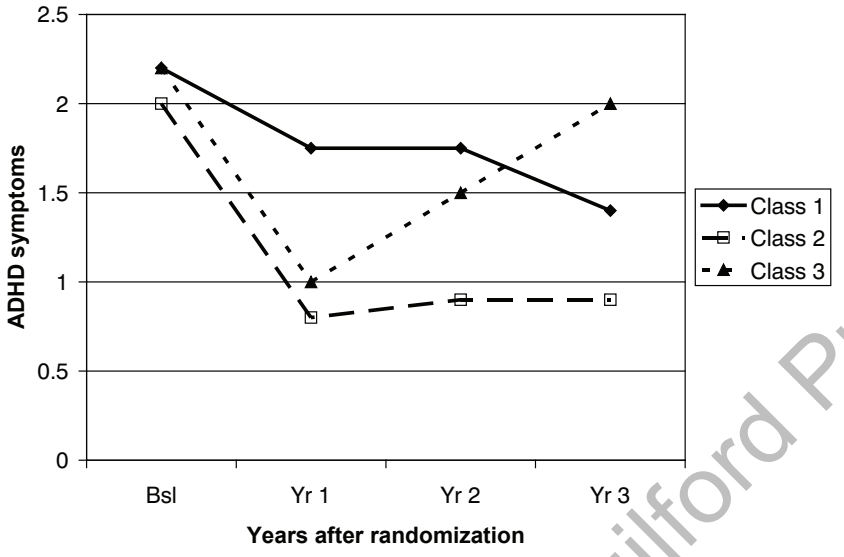

FIGURE 1.6. Three different types of outcome in the MTA study. From Swanson et al. (2007b). Copyright 2007 by Wolters Kluwer. Reprinted by permission.

Moving Forward

Given the wide variety of diagnoses that can be comorbid with ADHD, what is the most logical way to work through them? Many clinicians report what I have seen in my own practice: that severely dysregulated mood and aggression are the chief complaint in a growing number of cases. It therefore seems most prudent to begin with the study of the most common comorbidity in ADHD, that of ODD and CD. Dealing with oppositional and antisocial behavior invariably brings up the topic of aggression. Aggression, in turn, may be a symptom of other comorbid disorders, including sequelae of abuse, psychosis, and mania. Impulsive aggression may be a disorder separate from these, as in IED. Therefore, it would be best to step through these in an orderly manner: Chapter 2 deals with ODD and CD per se and emphasizes the differential diagnosis of irritability. It focuses also on behavioral approaches for ODD/CD to be used in combination with medication for the child's ADHD. Chapter 3 focuses on aggression more directly, particularly impulsive aggression in the absence of mood disorders. Since aggression of this sort is more common in children with a history of child abuse, this chapter is a good place to explore the treatment of children with ADHD who find themselves in foster care and not able to handle their placements due to their disruptive behavior.

Having explored the comorbidity of aggressive behavior, we are ready to move on to the diagnosis and management of patients with ADHD and bipolar disorder (Chapter 4). We then move on to the "internalizing disorders," such as depression (Chapter 5) and anxiety disorders (Chapter 6). The final two chapters concern tic and obsessive–compulsive disorders (Chapter 7) as well as developmental disorders such as intellectual disability (ID) and ASD (Chapter 8).

Case Material

Each chapter contains two to three cases from my clinical practice. To protect the privacy of patients, information not germane to the clinical situation has been removed or changed, including names, gender, and parent profession. Occasionally, composites were created from two or three very similar cases. I have not identified the ethnicity of patients to enhance protection of confidentiality, and I have used very common, nonethnic first names. In each chapter, the cases include some patients from more well-to-do families with plenty of resources, while others focus on families with very limited means and many psychosocial stressors. The point here is to show how comorbid disorders affect patients regardless of social standing, as well as how a clinician can respond in any of these settings. I have adopted another convention regarding generic or brand names of medication. In literature surveys about medications, I use generic names only. In the case reports, I use the brand name of the medication the child or adolescent was actually on. This allows a more realistic presentation of the case, and given the wide variety of the cases, the use of multiple brand names will be illustrated in a way that does not imply superiority of a particular brand when there is not scientific evidence to do so.