21 Children: Depression, Mania, and ADHD

Essential Concepts

- Depression in children is much more likely to herald bipolar illness than is depression in adults.
- Manic symptoms in children are often difficult to distinguish from attention deficit hyperactivity disorder (ADHD).
- Special attention should be given to family history in children as a key aspect of the diagnostic process.
- Amphetamines are biologically harmful in young animals; they should be used with caution in children, only in the absence of mood disorders, and for short-term treatment.
- Adult ADHD is likely an invalid diagnostic concept because it cannot be distinguished in adults from mood disorders. Applying the diagnostic hierarchy concept, independent adult ADHD symptoms are rare and not clearly separate from a population baseline of nonspecific cognitive impairment.

Depression is common in children, but perhaps the most important issue in children is differentiating unipolar from bipolar depression and differentiating bipolar disorder from attention deficit hyperactivity disorder (ADHD). It appears that children may differ in many ways from adults in the presentation of symptoms of bipolar disorder, as well as in their response to treatment.

MANIA

Diagnostically, the cardinal features of bipolar disorder are based on studies in adults. Those features are only newly studied in children. Based on the few studies available, though, the following generalizations can be made: The presentation of bipolar disorder in children differs between adolescents (age 12 and above) and nonadolescents. Most psychiatrists agree that bipolar disorder can be diagnosed adequately using standard adult criteria in adolescents. There is disagreement about whether it can be diagnosed in preadolescents. Available studies suggest that standard adult criteria are recognizable in adolescents. However, these adolescents demonstrate mainly mixed manic symptoms (about 80% of adolescents) rather than pure manic symptoms (about 40% of adults). Like adults, adolescents demonstrate periods of wellness in between periods of mood episodes. Since the manic phase is of the mixed variety, bipolar adolescents are predominantly depressed. They are depressed during their major depressive episodes, which can be lengthy, and they are depressed during their mixed episodes. To detect the difference, the clinician needs to rely on assessments of energy and other behaviors. In mixed episodes, bipolar adolescents are "wired," agitated, demonstrate decreased need for sleep, and are hyperactive. In pure major depressive states, they have low energy and are tired. The primary behavioral manifestations of mania in adolescence are sexual excesses. Since they are not adults, adolescents are simply not in a position to engage in some of the other standard behaviors, such as spending sprees, working excessively, or driving or traveling extensively.

Preadolescents, by contrast, often do not demonstrate the adult criteria for a manic episode. They do express symptoms of major depression, but maniclike symptoms consist mainly of irritability, agitation, hyperactivity, and violent or destructive behavior. These symptoms can occur in attention deficit disorder, as well as in nonspecific pediatric conditions such as Asperger syndrome or pervasive developmental disorder. When manic symptoms appear to be present, they seem to alternate with depressive symptoms in a rapid-cycling manner without any well intervals. Hence it can be difficult to identify manic symptoms owing to an inability to compare them with a euthymic baseline. Since preadolescent children generally do not engage in sexual behavior, they are not able to express

the sexual behavioral symptoms of mania, and like adolescents, they are, of course, unable to express the adult-related work, spending, and travel symptoms. Thus the only behavioral symptoms of note might be nonspecific hyperactivity and aggression, which, as noted earlier, is quite common in other pediatric conditions. Consequently, mania is difficult to diagnose based solely on symptoms in preadolescence, and many child psychiatrists refrain from making the bipolar diagnosis in this age group.

My view is that this controversy is based on excessive reliance on symptoms for diagnosis. As noted in Chapter 4, symptoms are only one of four criteria for diagnostic validity, the others being genetics, course, and treatment response. In my opinion, it is reasonable to assess a preadolescent child for depressive and irritable/aggressive symptoms and then to proceed to the other three criteria to attempt to differentiate incipient bipolar disorder from ADHD, pervasive developmental disorder, or other childhood conditions. The first, and perhaps most important, criterion to address after identifying the depressive/aggressive clinical picture is the family history. If a family history of bipolar disorder is present, especially in parents or siblings, then the likelihood of bipolar disorder in the depressive/aggressive preadolescent child is high. If a rapid-cycling course without a euthymic interval is present, then the course is consistent with the available empirical evidence on preadolescent bipolar disorder. Further, a trial of a mood stabilizer, alone or in combination with an antidepressant, can be informative regarding the likely diagnosis (although this is the weakest type of diagnostic evidence).

ADHD

The issue of differentiating preadolescent bipolar disorder from ADHD is particularly important. There are a few possibilities. One is that in some children, ADHD is simply a *forme fruste* (an atypical or mild variant condition) of bipolar disorder. By this, I mean that before adolescence, bipolar disorder is not able to be expressed in terms of adultlike symptoms. Children simply don't have credit cards with which to engage in spending sprees, they can't generally fly impulsively to different places, and they are not working at all, much less overworking. Neurodevelopmentally, they are also often not able to express mania in as typical or frequent a manner as is seen with symptoms in adults, such as flight of ideas, increased talkativeness, or other increased goal-directed activities. Perhaps in some persons, ADHD at age 6 is the manifestation of the same underlying neuropsychiatric abnormality that gets expressed as recurrent major depression from ages 10 to 16 and finally as mania alternating with depression from age 19 onward. There is some evidence for this forme fruste hypothesis. Recent studies suggest that 10% to 30% of adults with bipolar disorder appear to have experienced symptoms consistent with ADHD in childhood.

Another possibility is that some children have two separate and independent conditions, ADHD and bipolar disorder, that happen to overlap in some symptoms. A third possibility is that some children have ADHD only, and any bipolarlike symptoms are merely a manifestation of the ADHD.

As the old adage has it, in psychiatry, the course of illness is the pathology. In other medical disciplines, such a controversy could be answered by giving a specimen from the organ in question to the pathologist, who then would pronounce on the underlying illness. By and large, we are unable to do this in psychiatry, and thus the ultimate outcome is the best guide as to what actually exists. If a child appears to have ADHD, but it is really a forme fruste of bipolar illness, then that child will go on to develop manic and depressive episodes diagnosable with adult symptoms. If a child has both conditions, then bipolar symptoms will develop in adulthood, and ADHD symptoms frequently persist too. If a child has only ADHD, then adult bipolar symptoms never develop, and ADHD symptoms frequently resolve before adulthood.

Such long-term outcome is not available to parents or to child psychiatrists, however, who need to make decisions. There is no consensus, and I can only here suggest my opinions based on admittedly limited current research and experience. I think it is not unreasonable to take the following approach: First, emphasize the family history. If there is a family history of bipolar disorder, then the likely evolution of bipolar illness is quite high. Second, assess symptoms of irritability and aggressiveness; while not diagnostic, they tend to be more frequent in children with bipolar disorder, whereas classic ADHD without comorbid bipolar illness is not characterized by marked depression, dysphoria, aggression, or irritability. Third, assess treatment response. Since stimulants are used widely in the United States and are often effective for

ADHD but ineffective for bipolar illness, the attention paid to a possible bipolar diathesis should increase in stimulant-refractory children diagnosed with presumed ADHD. Fourth, when uncertain, follow the Hippocratic maxim of "First, do no harm." Stimulants can make bipolar illness worse, and thus where the ADHD diagnosis is vague and/or there is a suspicion of possible bipolar illness, stimulant use should be pursued less aggressively than in more obvious cases of pure ADHD. If bipolar illness is likely, then stimulants should be avoided and treatment initiated with mood stabilizers such as lithium or anticonvulsants, with or without concomitant atypical neuroleptic agents.

It is important to note also that amphetamine stimulants are far from benign. In fact, a number of animal studies have shown that amphetamine stimulants are harmful to the developing brain in rats; they lead to decreased hippocampal size, decreased dopaminergic activity, and increased corticosteroid response to stress. All these effects, it should be noted, are the opposite of the neurobiologic effects of antidepressants and lithium, which appear to be neuroprotective, leading to larger hippocampal size and decreased corticosteroid activity. In other words, amphetamine stimulants, neurobiologically, appear harmful to the brain, like drugs of abuse such as cocaine, and unlike most prescribed psychotropic medications. Further amphetamine use in adolescent animals has been associated with *higher* amounts of depressive and anxiety behavior in adulthood.

Obviously, these animal findings may not translate into humans, but we cannot assume that they will not, and these results, so at odds with most medications that are beneficial for mental illness, should give practitioners pause if they believe in a Hippocratic approach to medicine.

ADULT ADHD

It is now commonly accepted, in contrast to previous belief, that ADHD often persists into adulthood. The National Comorbidity Survey (NCS) estimates a 3% adult prevalence of ADHD versus about 7% in childhood. Thus one might conclude that about half the children with ADHD continue to experience those symptoms into adulthood. Some analyses of the NCS data indicate, however, that 86% of those adults diagnosable with ADHD are also diagnosable with either unipolar major depressive disorder or bipolar disorder. This

leaves us with two possibilities: Either almost all patients with adult ADHD also have mood disorders owing to the fact that they have very bad luck (or that these illnesses are always "comorbid"), or there is no such thing as adult ADHD. As discussed in Chapter 1 regarding the concept of a diagnostic hierarchy, one should not diagnose ADHD in the presence of active mood disorder. Thus the co-occurrence of the two should be interpreted as merely mood disorders with cognitive symptoms (i.e., concentration impairment in depression and distractibility in mania) unless proven otherwise. Unfortunately, many psychiatrists assume the reverse. They tend to always diagnose ADHD if any cognitive impairment with concentration is present.

If two sets of symptoms overlap 86% of the time, it does not make sense to me to persist in viewing those symptoms as separate, as opposed to one overall set of symptoms. Hence, if there is such a thing as adult ADHD, then we are referring to perhaps 14% (excluding the mood disorder overlap group) of the original 3% prevalence rate, which is 0.42%. What about this group? And what about the course-of-illness studies that indicate that many children with ADHD continue to have those symptoms into adulthood. Such course-of-illness studies are rarely controlled; I have found only one study that had a normal population control. Adults were examined for ADHD-like cognitive symptoms, and then their histories were examined for ADHD in childhood. The adults with ADHD-like symptoms who did *not* have a history of childhood ADHD were equal in percentage to the adults with ADHD-like symptoms who did have a history of childhood ADHD. In other words, there is a small baseline population rate of some attentional impairment that has nothing to do with previous ADHD in childhood that persists into adulthood. My view is that the small fraction that does not have mood disorders, the 0.42%, constitutes simply the baseline population that has some cognitive attentional impairment for nonspecific reasons unrelated to childhood ADHD.

What happens to childhood ADHD then? I believe that psychiatrists were more correct in our previous belief that it resolves than in our current belief that it persists. In most of children it seems to go away: Perhaps it was related to temporary neurodevelopmental disturbances or to psychosocial factors having to do with school or family stressors or the impact of poverty or class (as discussed earlier). In a minority of children, it persists but is transformed into mood

disorders or sometimes anxiety disorders as they typically present in adults. In other words, for such children, ADHD was a forme fruste of what later would develop into typical adult mood or anxiety disorders. In either case, there is no independent mental illness in adulthood called *adult ADHD* that would require separate diagnosis or treatment.

DEPRESSION

Separate from the issues of manic presentation and ADHD overlap, a more straightforward issue in children is the problem of depression. Children who develop major depressive episodes appear to have about a 50-50 chance of possessing either bipolar or unipolar illness. The bipolar illness may not become manifest until late adolescence or college years when a first manic/hypomanic episode occurs, however. Nonetheless, it is important to keep in mind that childhood depression is much more likely to represent an underlying bipolar illness than adult depression. The earlier the age of onset of depression, the less likely is the diagnosis of unipolar depression as opposed to bipolar depression. Again, a family history of bipolar disorder is the best predictor. In children with major depression and a family history of bipolar disorder, serious consideration again should be given to the use of lithium or anticonvulsants, with or without atypical neuroleptic agents. Antidepressant use may or may not be warranted, and if used, the antidepressant should be monitored carefully and perhaps may be best only for short-term purposes.

OVERDIAGNOSIS OF BIPOLAR DISORDER

In 2006, in Boston, a 4-year-old girl died after receiving the usual doses of three medications given for presumed bipolar disorder, diagnosed initially at age 3. This case led to a concern among many that bipolar disorder is being overdiagnosed in general and especially at unacceptably young ages.

In discussing this heated topic, I would first distinguish between diagnosis and treatment. The presence or absence of treatments for an illness, or their side effects, has no bearing on whether or not the illness is present: One may unfortunately

have cancer, even if its treatments are unbearable. It is hardly scientific to pretend that the diagnosis is different. Thus treatment concerns should be separated from the presence of an illness. In the case of bipolar disorder, I want to be clear that I am not advocating widespread diagnosis in children based on vague symptoms such as "mood swings."

USING MOOD STABILIZERS IN CHILDREN

The usual reaction I receive from colleagues when I describe the preceding viewpoints is a reaction that mood stabilizers are too toxic to use in kids. Even if this is the case, which in many cases it is not, again, this issue has no bearing on whether or not children have the diagnosis. It only has bearing on what we do about it.

My view is that we need to hold fast to Holmes' rule: All medications are toxic, and all should be presumed to be so even if we have limited evidence; the key is whether they are effective and whether the benefits of that efficacy outweigh their toxicity.

In the case of "safe" drugs such as serotonin reuptake inhibitor (SRI) antidepressants, they clearly are not appropriate at least in monotherapy for bipolar disorder; thus no efficacy plus some side effects lead to a risk-benefit assessment that would argue against their use.

In the case of amphetamine stimulants, they too are not effective because they are antidepressants and thus carry the same risks and lack of mood-stabilization benefit as standard antidepressants. Not only that, but they also appear to be harmful to the developing brain. No benefits and notable risk (although often underappreciated) again would argue against using these agents.

Many clinicians turn to atypical antipsychotics as an alternative (anything, it seems, to avoid real mood stabilizers). Yet there are zero randomized maintenance studies of such antipsychotics in children with bipolar disorder. This is hardly evidence-based medicine. Some have been shown to be effective in acute mania, although none has been studied in acute depression in children. They also have risks: some with obesity and metabolic syndrome, all with extrapyramidal symptoms, and most with limited long-term data on their neurobiological effects. Again, except for possible short-term

use for acute mania, we have no evidence of efficacy in long-term treatment and moderate or greater risks.

This leaves us with the mood stabilizers, lithium and divalproex Lamotrigine has been studied in epilepsy but not in bipolar disorder in children, and carbamazepine only has observational evidence.

In the face of ignorance, we should be even more cautions with medication treatment of children. If medications are used, I would lean toward extrapolation from adult data, which support lithium and anticonvulsants (not antipsychotics) is mood stabilizers.

One way to manage the reticence to use lithium or divalproex owing to side effects is to consider using low levels of these agents. Their therapeutic blood levels are established in nonelderly adults; their levels may vary with age. We know that in the elderly, lower lithium levels usually are required. Similarly, in preadolescent children, owing to the increased sensitivity of the developing brain, it may be wise to use low levels of lithium (0.4 to 0.6 ng/dL) or divalproex (30 to 60 ng/dL) at least initially. In this way, the treatment decision is not necessarily an all-or-nothing matter of deciding to take high doses of lithium or divalproex. Lower levels are associated with fewer side effects and thus will be more tolerable. In many preadolescent children, especially those with atypical and less severe manic features, low levels may be sufficient to improve depressive symptoms without causing mania or to improve mixed presentations. If the child tolerates low levels of mood stabilizers but does not improve much, then the doses can be increased to standard therapeutic levels. There are no studies of this idea, but in my view, it is safer and more rational than the equally unproven options of atypical antipsychotic or antidepressant use.

THE TOM CRUISE EFFECT

I am aware that some of my views, especially regarding ADHD, will be viewed by many psychiatrists with suspicion. Once, after my discussion of the likely invalidity of adult ADHD, a colleague at one of my lectures commented that I sounded like the actor Tom Cruise. Indeed, the whole topic of ADHD is burdened with what I call the "Tom Cruise effect," which is when any critique is viewed defensively by psychiatrists as a dogmatic attack on psychiatry as a

profession. This is not my intention at all. I think, in fact, that our profession gives its critics plenty of fodder for such attacks by unthinkingly embracing new fads such as the adult ADHD diagnosis and downplaying real biological evidence for the harms of amphetamine stimulants. I hope colleagues will read this chapter with an open mind, acknowledging that not only many of my ideas but also many of their ideas could be wrong.