Addressing Comorbidity in Adults
With Attention-Deficit/Hyperactivity Disorder

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Psychiatric comorbidity complicates the accurate diagnosis and effective treatment of attention-deficit/hyperactivity disorder (ADHD) in adults. This paper examines the influence of comorbidity on treatment responsiveness in ADHD adults, the neurobiological underpinnings of comorbidity, and the potential of different pharmacologic agents to address comorbid states in ADHD. A categorical schema for neurobiological classification of ADHD subtypes is integrated with literature associating specific neurotransmitters with corresponding neurobehavioral abnormalities. Dopamine, for example, is one of several neurotransmitters implicated in bipolar disorder. Serotonin and norepinephrine are implicated in major depression and anxiety disorders, while self-medication for dopamine dysfunction may relate to substance abuse. Norepinephrine and serotonin have each been linked to aggression and impulsive antisocial behaviors. The effective treatment of ADHD with comorbid psychiatric disorders requires knowledge of the neurochemical underpinnings of each disorder and expertise in the application of appropriate pharmacologic tools. Controlled studies assessing treatment outcomes for both comorbid disorders will assist in the development of improved treatment strategies for adults with complicated ADHD. *(J Clin Psychiatry 1998;59[suppl 7]:69–75)*

Psychiatric comorbidity complicates the accurate diagnosis and effective treatment of attention-deficit/hyperactivity disorder (ADHD) in both adult and pediatric populations.[1,2] From a clinical standpoint, the excess in symptom complexity contributed by the comorbid disorder hinders diagnostic precision. From the neurobiological perspective, psychostimulants—long considered the treatment of choice for ADHD[2,3]—may exacerbate the symptoms of psychiatric disorders that frequently coexist with ADHD, such as anxiety and affective disorders,[3] or may fail to treat the comorbid condition.[4] However, with other comorbid disorders, Shekim et al.[5] and Wender and colleagues[6] found that the presence of a substance use disorder did not affect the response of ADHD symptoms to stimulants. Thus, consideration of additional disorders potentially comorbid with ADHD and establishment of more comprehensive pharmacologic treatment algorithms to address comorbid pathology are clearly warranted.

It has long been recognized that symptoms of ADD persist into adulthood.[7–9] Even so, ADHD remains underdiagnosed in adult populations,[10–12] although recent media attention has perhaps created an excessive willingness on the part of the general public to embrace this disorder. At least in part, issues regarding comorbidity may play a role. In ADHD patients with comorbid affective disorders, for instance, isolated symptoms of hyperactivity or impulsivity may arise solely from an atypical hypomania or mania. Likewise, the inattentiveness or poor concentration commonly attributed to ADHD might be due to the cognitive disturbance of a depressive episode. Impulsive behavior may be misattributed to an antisocial or borderline personality structure. Adult ADHD patients with any of these comorbid disorders require disparate treatment considerations. Making diagnostic sense of the wide variety of clinical presentations in patients with comorbid disorders is critical to ultimate success in treatment.

This paper will briefly review the available literature concerning the diagnosis and prevalence of comorbid disorders in adult ADHD populations, drawing inferences from the pediatric literature. For each type of psychiatric disorder that may coexist with ADHD, neurobiological substrates and the implications of these neural disturbances for making informed treatment choices in the adult patient with ADHD will be considered. Pharmacologic studies specifically addressing treatment issues in adults with complicated ADHD will be noted where available.

DIAGNOSIS AND EPIDEMIOLOGY OF ADHD AND COMORBID PSYCHIATRIC DISORDERS IN ADULTS

Psychiatric comorbidity in patients with ADHD creates a plethora of symptoms, rendering it difficult to identify which specific symptom clusters arise from each condition. Structured clinical interviews[13] may prompt overdiagnosis as a result of literal translations of DSM-IV criteria[14] that attribute overlapping symptoms to two (or more) comorbid disorders. Reducing symptom complexity to the lowest common denominator requires a comprehensive appreciation of patterns of comorbidity in ADHD populations. In adults, few studies assist in this diagnostic dissection. In one study of referred and nonreferred adults with ADHD, Biederman and colleagues[15] found a pattern of comorbid psychopathology similar to that observed in pediatric populations. Seventy-seven percent met criteria for at least 1 of 17 comorbid psychiatric disorders. As in pediatric populations, affective, anxiety, substance abuse, and learning disorders are the most frequently diagnosed comorbid Axis I conditions among adults with ADHD. Persistence of ADHD into adulthood appears more likely to be compounded by psychiatric comorbidity.[16] In studies of referred and nonreferred adults with ADHD, such associations do not appear to be an artifact of overlapping symptoms, as diagnoses of generalized anxiety disorder, major depression, and bipolar disorder are maintained even when overlapping symptoms are subtracted.[17,18]

Failure to diagnose ADHD in adults also relates to realistic concerns about prescribing controlled substances to patients who may have a history of substance abuse or antisocial personality disorder. In addition, no widely accepted, proven, efficacious alternatives to controlled substances are available. Six controlled studies of stimulants in adult ADHD reported response rates varying from 25% to 78% with an average of 54%,[3,6,9,10,19–21] comparable to rates reported for pediatric populations.[3] Nonetheless, the capacity of stimulants to address comorbid conditions such as depressive and anxiety disorders may be reduced,[4] and there is some indication that the response of even ADHD symptoms to stimulants may be decreased in complicated ADHD.[3] However, another study by Spencer and colleagues[10] suggested that the response of ADHD symptoms to methylphenidate is independent of the presence of a comorbid disorder. Because the response of the symptoms of the comorbid disorder to methylphenidate was not directly assessed, the potential of methylphenidate to control such symptoms is unclear.

Other potent psychostimulants, such as dextro- and methamphetamine, are used even less frequently than methylphenidate and have been less frequently studied in clinical trials due to regulatory concerns. Magnesium pemoline, a predominantly dopaminergic agent[22] with Schedule IV classification by the Drug Enforcement Agency,[23] has fewer regulatory controls but a lower response rate than other psychostimulants.[1] High doses may elicit a greater response rate but risk hepatic toxicity.[22] Selegiline, a monoamine oxidase-B inhibitor (MAOI-B) metabolized to levoamphetamine and levomethamphetamine in addition to desmethylselegiline,[24] has not been extensively explored in controlled trials for efficacy in adult ADHD, and no studies directly assessed patients with comorbid conditions. Although studies suggest its cognitive enhancement potential in animals,[25] effects in adult ADHD are less certain.[26] In children selegiline may play a role in the treatment of comorbid Tourette's disorder and ADHD.[27,28]

Stimulants such as dextroamphetamine may possess relatively greater dopaminergic than noradrenergic potency, whereas methylphenidate's potency appears relatively stronger in noradrenergic than in dopaminergic systems.[29] Such distinctions in effects on different neurotransmitter systems may relate to dextroamphetamine's greater potential for abuse. It remains undetermined, however, whether such differences in neurochemical profile are associated with differences in clinical efficacy, particularly regarding psychiatric comorbidity. Development of nonstimulant alternatives with the capacity to address both the symptoms of ADHD and the comorbid condition may produce clinical outcomes of greater overall benefit to the patient with complicated ADHD.

NEUROBIOLOGICAL SUBSTRATES OF COMORBIDITY IN ADHD

Understanding the regional neurotransmitter dysfunction underlying symptoms of ADHD and the comorbid disorders associated with such neurochemical changes can help guide more effective pharmacotherapy for both attentional and comorbid conditions. Although it is unlikely that any one psychiatric disorder is linked purely to dysfunction in a single neurotransmitter system, and multiple levels of interaction among neuromodulators are likely to be important, specific neurotransmitters such as serotonin (5-HT), norepinephrine (NE), dopamine (DA), and γ-aminobutyric acid (GABA) are strongly associated with specific types of behavioral abnormalities. Furthermore, while classical models of ADHD[30] focus primarily on DA and NE dysfunction, there is increasing evidence that 5-HT systems may be abnormal in some subsets of ADHD populations.[31] Such links may provide clues to the types of pharmacologic interventions that may be most helpful in addressing ADHD comorbidity.

Whereas NE and 5-HT neurotransmitter systems are classically linked to major depressive disorder (MDD), recent evidence[32] suggests an association with DA dysfunction in some patients with mood disorders. DA systems are additionally linked to substance use disorders through effects on reward circuitry, including nucleus accum-

bens.[33–35] Serotonin system abnormalities have also been connected to aggression and impulsivity[36] and to anxiety disorders,[37] while norepinephrine and GABA disturbances are additionally linked to anxiety symptoms.[37] Thus, a shared neurochemical substrate may explain the observed link between ADHD and many comorbid disorders.

A CATEGORICAL SCHEMA FOR ADHD SYMPTOMS

A heuristic schema based on the neurobiological, neurochemical, and neurobehavioral features of ADHD has been suggested by Robert D. Hunt, M.D., who divides the wide variety of ADHD symptoms into four major categories: (1) cognitive-processing deficit, (2) excessive arousal, (3) impaired behavioral inhibition, and (4) deficient reward systems.[38] Hunt's proposal that different neurotransmitters may underlie these subtypes of ADHD forms the basis for rational pharmacologic approaches to the complex symptom spectrum observed in ADHD. Many of the conditions frequently comorbid with ADHD, such as depression and anxiety disorders, are also associated with symptoms in each of these four categories.

Cognitive-Processing Deficit System

The first subtype described by Hunt focuses on deficiencies of cognitive and perceptual processing systems. The cognitive-processing deficit subtype is primarily a disorder of selective attention and information processing and possibly related to hypoactivity of the dopamine system. In particular, the gating capacity of the nucleus accumbens, stimulus processing and analysis functions of cortical sensory integration centers, the ability of the hippocampus to identify change in the environment, and response selection capacities of the prefrontal cortex are thought to be involved. Learning disabilities and mental retardation are common correlates. Dopaminergic agents such as the stimulants are thought to address this symptom cluster.

Excessive Arousal System

The symptoms observed in the excessively aroused patient subtype are thought to relate to hyperactivity of noradrenergic circuitry, involving the locus ceruleus and the reticular activating system. Major symptoms of the over-aroused subtype include increased motor activity, difficulties with sustained attention, impulsivity, and aggression. Comorbid disorders commonly seen with this subtype are conduct disorder and mania. Noradrenergic antagonists with effects at α_2 receptors, including clonidine and guanfacine, are thought to be effective. Additionally, tricyclic antidepressants (TCAs) may be beneficial for this subtype due to their predominantly noradrenergic action. Although not specifically addressed by Hunt's review, anxiolytic GABAergic agents such as benzodiazepines

may also be capable of combatting the psychological and somatic overarousal associated with this subtype of ADHD.

Impaired Behavioral Inhibition System

The third symptom cluster noted in Hunt's schema, impaired behavioral inhibition, is thought to arise from the combined dysfunction of serotonergic and dopaminergic circuits in the prefrontal cortex and in subcortical regions (e.g., the caudate nucleus, the thalamus). Serotonin deficits seem to relate most directly to impulsivity via prefrontal cortical circuits, while the difficulties with response selection associated with DA dysfunction are thought to be linked to abnormalities in neural circuits affecting both the striatum and prefrontal cortex. Were a single pharmacologic agent available to address both the 5-HT and the DA abnormalities of this subtype, Hunt hypothesizes that it would have neurobehavioral effects diametric to those of clomipramine, *increasing* obsessionality and behavioral inhibition. However, as mounting evidence suggests both that impulse control disorders may be improved by agents with potent 5-HT effects[37] and that the putative DA component of this symptom cluster (i.e., response selection abnormalities) might be addressed through the use of a psychostimulant in addition, the combination of an agent with 5-HT and DA-enhancing effects may be indicated. Agents such as the MAOIs, high-dose venlafaxine (a 5-HT and NE reuptake inhibitor with weak DA effects), or a serotonin selective reuptake inhibitor (SSRI) combined with a stimulant may be helpful.

Deficient Reward System

Hunt's final symptom cluster is the deficient reward system. Difficulties in affect regulation, presumably arising from defects in limbic circuitry, lead to emotional remoteness and indifference to reward or punishment, and faulty cognitive analysis and integration of information arise from defects in prefrontal and associative cortex. Although Hunt implicates endorphins and other neuropeptides in the control of these behaviors, much evidence supports the role of DA and the nucleus accumbens in reward mechanisms,[33–35] and on this basis a trial of a psychostimulant with strong DA effects such as dextro- or methamphetamine is suggested.

PHARMACOLOGIC MANAGEMENT OF DISORDERS COMORBID WITH ADHD

Affective Disorders

Estimates of the comorbidity of mood disorders with ADHD in children run from 15% to 75%.[39] Similar patterns are thought to exist in adults.[15] In referred adults with ADHD, major depressive disorder (MDD) was present in 31%; in nonreferred ADHD adults, MDD was present at a slightly lower rate (17%).[15] A study by Alpert and col-

leagues[40] found that 16% of outpatients presenting for treatment of MDD met at least subthreshold criteria for a DSM-III-R diagnosis of childhood ADHD, and nearly 75% of these patients noted the persistence of ADHD symptoms into adulthood. Ratey et al.[41] found a substantially higher rate; nearly half of 60 adult outpatients presenting for treatment of MDD met ADHD criteria.[41] Similar patterns of comorbidity were noted by Shekim et al.,[5] who found a historical diagnosis of MDD in 10%, hypomania in 4%, dysthymia in 25%, and cyclothymia in another 25% of adults with ADHD.[5] Some patients with adult ADHD may also present with chronic or treatment-resistant depression.[21,42]

That ADHD symptoms in children and adolescents respond to TCAs is well documented.[10] Several controlled trials now corroborate this response in adults.[3,43] Response of ADHD symptoms to TCAs appears to be independent of current or past psychiatric comorbidity; however, the response of comorbid mood disorder symptoms has not been routinely assessed.[43] In children, TCAs are thought to be more effective in behavioral disturbances such as hyperactivity and impulsivity than in cognitive problems[44]; they may be preferentially effective for concomitant anxiety, depression, or tics.[3] The ability of TCAs to ameliorate behavioral dysfunction may relate to their predominantly norepinephrine-based actions,[45] but their anticholinergic actions might reduce cognitive function.[46,47] Daily doses as high as 3.0 mg/kg of desipramine are thought to be the effective range for adults with ADHD.[43]

An early report by Wender and colleagues[21] noted that the reactive mood disorder often accompanying ADHD in their adult population appeared consistent with so-called "atypical depression." Such atypical depressions may respond poorly to TCAs but exceptionally well to agents with potent DA activity, including the MAOIs.[48] Wender et al. posit that patients with comorbid ADD and atypical depression might also be selective responders to dopaminergic psychostimulants as well as to MAOIs, with benefit for symptoms of both disorders.[21] This subtype of depression is thought to be more common in patients with bipolar disorder.

Comorbidity of ADHD and bipolar mood disorder subtypes has been reported as quite high. Ninety-eight percent of children with mania also met DSM-III-R criteria for ADHD in one study[49]; in addition, this group had high rates of major depression, psychosis, and anxiety and conduct disorders. Such comorbidity is apparently common: studies indicate both an increased incidence of ADHD in families of bipolar probands,[50] and increased bipolar disorder in families of ADHD probands.[51] In addition, in one study 65% of patients with onset of bipolar disorder symptoms by age 18 had a diagnosis of ADHD versus 0% of patients with onset of symptoms of bipolar disorder after age 18.[52] As noted earlier, such associations do not appear to be an artifact of overlapping symptoms, as diagnoses of

bipolar disorder are maintained even when overlapping symptoms are removed.[17,18] However, treatment of adults with comorbid ADHD and bipolar disorder has not been systematically evaluated.

DA is one of several neurotransmitters linked to bipolar disorder.[53] Agents with potent DA effects, including the psychostimulants, the MAOIs, and direct DA agonists (e.g., levodopa, bromocriptine) might be of short-term benefit for the treatment of nonpsychotic bipolar depressions if administered with lithium or other mood stabilizers to prevent the induction of mania. At typical doses, bupropion is thought to act primarily via noradrenergic system effects, and it is only at chronic, high doses that bupropion may also influence DA circuitry (e.g., the nucleus accumbens and areas A9 and A10 of the ventral tegmentum).[54] Venlafaxine, in contrast, is reported to have mild DA effects even in the usual dose range, although the clinical significance of such neuropharmacologic effects is unclear.

Bupropion has been reported effective for ADHD in adults. Wender and Reimherr[55] found improvement in 14 of 19 adult ADHD patients on a mean daily dose of 360 mg. Although these patients were not diagnosed with comorbid MDD, mood symptoms that were present as part of their ADHD symptom complex showed greater improvement than symptoms of inattention, hyperactivity, and impulsivity. Nonetheless, 9 of 14 improved patients showed additional progress over a 1-year period. Dosages of 50 to 150 mg three times daily have typically been employed, although at least one report notes response to much lower doses of bupropion (18.75 mg t.i.d.).[2] Patients with bipolar I or rapid-cycling bipolar disorder are thought to be candidates for bupropion therapy when antidepressant therapy is indicated, as some early studies indicated a lower risk of the induction of hypomania or mania in these populations than with other antidepressants.[56,57] Other studies indicate a risk of manic induction comparable with other antidepressants,[58] although affective disruption may be less severe.[59] Although no controlled studies are available in bipolar populations, bupropion may play a role in the treatment of the ADHD patient with a comorbid bipolar condition. The inclusion of mood stabilizers such as lithium, carbamazepine, or divalproex is recommended as it would be for any bipolar patient but will not uniformly guarantee protection against manic breakthrough symptoms.[58] Based on its pharmacology, bupropion might play a general role in the treatment of the excessively aroused, NE-based ADHD subtype with psychiatric complications.

Venlafaxine, a phenylethylamine with a chemical structure similar to dextroamphetamine, is a potent 5-HT and NE reuptake inhibitor with weak DA reuptake inhibitory properties.[60,61] In several open-label studies of adults with ADHD, venlafaxine has been effective in controlling ADHD symptoms.[62–65] In addition, 80% of patients with

comorbid ADHD and MDD showed improvement in both their depressive and their attentional symptoms; only 33% of patients receiving stimulant monotherapy improved in both comorbid disorders.[42] Although the efficacy of venlafaxine in addressing both ADHD and MDD symptoms may be traced in part to its 5-HT, NE, and/or weak DA properties, its phenylethylamine structure may also be a key factor in its effects. Based on its potent NE and 5-HT properties, venlafaxine is hypothesized to have its greatest benefit for the excessively aroused and impaired behavioral inhibition subtypes, but its DA component, however weak, might also help to alleviate symptoms seen in the other two ADHD subtypes (e.g., the cognitive processing and deficient reward system subtypes).

Anxiety Disorders

Fifty-three percent of adult ADHD patients evaluated by Shekim and colleagues[5] met criteria for generalized anxiety disorder, 15% for panic disorder, 13% for obsessive-compulsive disorder (OCD), and 8% for phobias. Similarly, 32% of adult ADHD patients in Murphy and Barkley's sample[11] met DSM-III-R criteria for anxiety disorders. Given the substantial overlap in the somatic aspects of the excessively aroused subtype of ADHD and the somatic manifestations of many anxiety disorders (e.g., panic disorder, generalized anxiety disorder), similar agents might address both types of disorders. The role of NE-based agents, such as the TCAs, in addressing the NE-mediated aspects of hyperactivity and impulsivity symptoms of ADHD is reviewed in the section above on affective disorders. Although changes in anxiety symptoms were not directly assessed, a 6-week placebo-controlled trial of desipramine found that the response to this noradrenergic TCA was independent of the presence of an anxiety disorder comorbid with ADHD.[43] For comorbidity of anxiety disorders such as OCD, a 5-HT-based agent beneficial for OCD symptoms (e.g., serotonin selective reuptake inhibitors, clomipramine) might also help control the 5-HT-mediated aspects of ADHD-related impulsivity.

Alcohol and Substance Abuse Disorders

Psychoactive substance use disorders occur at a higher rate in adult patients currently or previously meeting criteria for ADD than in the general population.[66–69] Biederman and colleagues[66] found that both drug and drug-plus-alcohol use disorders occurred at a higher rate in referred adults with ADHD (52%) compared with control populations (27%), although these two groups did not differ in rates of alcohol use alone. The increased risk for substance use disorders was independent of psychiatric comorbidity, although the presence of mood, anxiety, or antisocial personality disorders further increased the risk. Marijuana use was most common, followed distantly by cocaine and stimulants.[66] Despite data consistent with the self-medication hypothesis of substance use disorders,[70]

rates of psychostimulant use were not high in patients with ADHD in this study.

In certain individuals, however, cocaine abuse appears to be related to an attempt to self-medicate for DA dysfunction; such patients may demonstrate improvement in both ADD symptoms and in cocaine use with the DA agonist bromocriptine[71] or with methylphenidate.[72] Dopamine's role in mediating the reinforcing effects of cocaine may suggest a mechanism by which such treatment responses might be understood.[73,74]

Nicotine dependence also occurs at higher rates in ADHD populations.[75,76] Interactions of nicotine with DA system abnormalities may be important in understanding the neuropharmacology of ADHD. The effects of nicotine on brain areas involved in the regulation of impulsive behaviors, such as the caudate nucleus, are mediated mostly by D_1 receptors.[77] In the brains of living smokers,[78] monoamine oxidase-B is inhibited, increasing DA availability in the brain. In addition, nicotine dependence occurs at high rates in mood disordered populations[79] and mood disorders frequently emerge or reemerge with smoking cessation,[80] suggesting a neuropharmacologic basis for comorbidity. Although no published studies report the administration of nicotine in depressed ADHD patients, trials of transdermal nicotine in ADHD patients (both smokers who had been abstinent for at least 24 hours and nonsmokers)[81,82] and in nonsmoking patients with major depression[83] were effective, further suggesting a shared neurochemical basis for both disorders.

Tourette's and Tic Disorders

Few to no data concern the response profiles of adult patients with ADHD and tic or full-blown Tourette's disorders to various stimulant or nonstimulant agents for the treatment of ADHD. In children, Gadow and associates[84] found a weak overall influence of methyphenidate on tics, with a trend toward increased motor and decreased vocal tics. Bupropion, an agent with potent NE and possibly weak DA effects,[54] has demonstrated benefit for ADHD children[85] and adults[55] but exacerbates tics in studies of children with comorbid ADHD and Tourette's disorder.[86] As noted earlier, in children with comorbid Tourette's disorder and ADHD, selegiline may be somewhat effective for both disorders.[27,28]

Antisocial Personality Disorder

High-dose β-blockers may hold some promise for treatment of aggression in the ADD patient, presumably by blocking postsynaptic NE receptors. Mattes[87] noted a decrease in angry outbursts in 11 of 13 adult ADD patients on a mean daily dose of 538 mg of propranolol.[87] Two studies[88,89] have reported 20 to 80 mg per day of nadolol effective in combination with stimulants for ADHD with aggressivity.[88,89] A case series by a Norwegian group indicated that stimulant medication was effective for ADHD

symptoms in five prisoners with a history of violent crimes; two were successfully rehabilitated after a period of treatment.[90] Impulsive aggression is thought also to relate to 5-HT dysfunction and may be inhibited by SSRIs or other agents with potent 5-HT system influence.[91] Addressing ADHD symptoms in antisocial populations with β-blockers, stimulants, or serotonergic agents may provide greater control of impulsive antisocial behaviors.

SUMMARY

The treatment of the adult with ADHD and comorbid psychiatric conditions requires a complex appreciation of the neurochemical underpinnings of each of the disorders and expertise in the application of appropriate neuropharmacologic tools for addressing such neurochemical derangements. Although general patterns of comorbidity appear to be similar to those in children, comorbidity may be an even more common phenomenon in adults with ADHD. Thus, controlled studies evaluating clinical outcomes for *both* comorbid disorders following various treatment strategies are critical to effective treatment of adults with ADHD.

Drug names: bromocriptine (Parlodel), bupropion (Wellbutrin), carbamazepine (Tegretol and others), clomipramine (Anafranil), clonidine (Catapres), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), divalproex (Depakote), dopamine (Dopastat, Intropin), guanfacine (Tenex), levodopa (Larodopa), magnesium pemoline (Cylert), methamphetamine (Desoxyn), methylphenidate (Ritalin), nadolol (Corgard), propranolol (Inderal and others), selegiline (Eldepryl), venlafaxine (Effexor).

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