Mood Disturbance in ADHD Due to a General Medical Condition

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John G. Ryder and Jacquelyn M. Silva

The medical evaluation of mood disturbance in patients diagnosed with ADHD, like all great quests, begins with a clear definition of what is being pursued. Taber's cyclopedic medical dictionary defines mood as "a pervasive and sustained emotion that may have a major influence on a person's perception of the world" [1]. The use of the word "sustained" highlights the importance of considering an emotion's duration when defining a particular mood state. Duration is partially determined by the individual's ability to self-regulate emotions, which is a complex learned process. In brief, it is the ability to emotionally respond to the demands of an experience in a manner that is socially normative. Furthermore, the person must demonstrate enough flexibility to willfully permit or deny spontaneous reactions to that experience such that dysfunction does not occur (non-pathological response) [2]. There is a significant association between an inability to do this—emotional dysregulation, and mental disorders for which a disturbance in mood is their primary feature (mood disorders) [3, 4].

In the process of formulating a differential diagnosis, clinicians are often readily alerted to the importance of evaluating for organic causes of new psychiatric presentations, such as depression or anxiety, when they correlate with the onset or exacerbation of a general medical condition. However, sometimes emotional dysregulation is the only harbinger of an insidious mood disorder that may be present or emerging.

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Irritability and emotional lability are two major components of emotional dysregulation and subsequently mood dysregulation to be vigilant for in all patients [5, 6]. Mood and anxiety disorders often coexist with medical conditions, and practically all psychiatric symptoms can be mimicked by a general medical condition. In some patients these disorders can contribute to the medical condition, whereas for others the medical condition is the underlying cause. It is important to be aware that symptoms of depression, irritability, mood lability, and anxiety can be prodromal of medical illness that if not uncovered early, could lead to significant morbidity and mortality.

For instance, in patients with carcinoma of the pancreas, symptoms of depression (affecting 38% to 45% of patients) and anxiety (affecting about 12% of patients) are among the earliest disease manifestations [7]. Endocrine tumors producing adrenaline such as pheochromocytomas are often heralded by panic attacks, anxiety, and irritability [8, 9]. Physical symptoms of hyperthyroidism such as sensitivity to heat, weight loss, restlessness, and sleeping difficulty can mimic an anxiety disorder, and irritability can also be an early disease manifestation [10]. Untreated streptococcal infection may lead to the onset of movements/tics called Sydenham's chorea. In studies of children with Sydenham's chorea, they exhibited obsessive-compulsive symptomatology, increased emotional lability, motoric hyperactivity, irritability, distractibility, and age-regressed behavior [11]. It is well known that irritability, anxiety, depression, dementia, and psychosis are associated with vitamin B12 deficiency [12]. Head injuries can cause post-concussive symptoms that develop within days of the incident and can last anywhere from a couple of days to a few months. These symptoms can mimic depression, anxiety, and attention-deficit disorders [13]. School failure, cognitive loss, hyperactivity, aggression, inattention, distractibility, and delinquent behaviors have all been reported with lead poisoning [14]. There truly is a myriad of general medical conditions associated with, and producing, psychiatric symptoms.

With this in mind, clinicians have an important role in managing the complete care of their patients. Patients with general medical conditions and associated psychiatric symptoms often suffer twice. MEND A MIND is a well-known useful mnemonic for ensuring a broad differential for organic causes of psychiatric presentations and can aid the clinician when evaluating a patient [15]. The mnemonic, which is slightly modified here to consider drugs/intoxication before degenerative causes (given the rarity in children) stands for: **M**etabolic/endocrine, **E**lectrical (seizures) **N**eoplastic, **D**rugs/intoxication, **A**rterial/venous, **M**echanical (trauma), **I**nfectious/inflammation, **N**utrition, **D**egenerative. The following table lists common organic causes of mood disturbance in order of the mnemonic, and provides general (by no means exhaustive) workup approaches to evaluation. The table applies to adults as well as children, but there is an emphasis here on the pediatric population with ADHD. See Table 3.1.

Table 3.1 Organic causes of mood disturbance in children and adults with ADHD

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Metabolic and endocrine	
Abnormal glucose [16, 17]	
• Malaise, lethargy • Polyuria, polydipsia, polyphagia • Weight gain/obesity or weight loss • Acanthosis nigricans	– BMI, blood pressure – Evaluate for orthopedic complications: hyperlordosis, pes planus, genu valgum – Fasting glucose/HgbA1C – Total cholesterol, HDL cholesterol, LDL cholesterol – TSH
Thyroid abnormality [18, 19]	
• Children may appear to be asymptomatic • Family history of thyroid abnormalities	– Physical examination of the thyroid gland – TSH, free T4 if TSH is abnormal – Consider confirmatory TSH – Consider total T3, T4
Calcium abnormality [20, 21]	
• Hypo: tetany, paresthesia, cramping, altered mental status, seizures, laryngospasm, cardiac arrhythmias, neuromuscular irritability with weakness, ECG changes (prolonged QT interval) • Hyper: weakness, irritability, lethargy, seizures, abdominal cramping, lethargy, seizures, vomiting, polyuria, polydipsia, renal calculi, ECG changes (atrial and ventricular ectopy, torsades de pointes)	– Trousseau sign – Total and ionized Ca^{2+}, Mg^{2+}, phosphate – Alkaline phosphatase – Total protein – BUN – Creatinine – 25-OH vitamin D – Parathyroid hormone level – Urine: Ca^{2+}, phosphate, creatinine – ECG
Electrolyte abnormality [22]	
• Emesis, acute/chronic diarrhea • Dry mucus membranes, delayed capillary refill (i.e., >2 seconds) • Tachycardia • Diabetes mellitus	– Screen for infectious illness, food poisoning, and diabetes – Physical exam assessing for dehydration – POCT glucose – Basic metabolic panel
Sleep-related hypoxia [23, 24]	
• Male sex, overweight • Household smoking, history of asthma, respiratory allergy, current respiratory tract infection • Symptoms of sleep-disordered breathing (e.g., habitual snoring or gasping while • Enlarged tonsils and/or adenoids	– Sleep hygiene history – BMI, HEENT and pulmonary physical exam – Consider sleep medicine referral – Consider ENT referral
Addison's disease (chronic primary adrenal insufficiency) [25]	
• Malaise • Anorexia, weight loss • Diarrhea • Joint and back pain • Darkening of the skin	– Rule out by history, labs, and/or other studies: tuberculosis, histoplasmosis, coccidiomycosis, blastomycosis, CMV, MAC – Evaluate for autoimmune disease – Screen for neoplasm (lung, kidney, gut, primary lymphoma)

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Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Electrical	
Temporal lobe epilepsy/status epilepticus [26–29]	
• Reading difficulty (patient may be less responsive to reading treatments) • Verbal semantic and episodic memory impairment, déjà vu • Abdominal discomfort, sudden intense emotion, abnormal mouth movements, rhythmic muscle contractions	– Neurological physical exam – Check electrolytes – Consider brain imaging – EEG
Neoplastic	
CNS tumors (primary and metastatic) [30–32]	
• Headache, seizures, nausea/vomiting • Behavioral changes (irritability, mood, character, school), sleep disturbance • Neurologic deficits: ataxia, squint, diplopia, papilledema, visual loss, cranial neuropathy, head tilt, hemiparesis • Lethargy, anorexia, weight loss, polyuria, polydipsia, dizziness • Growth failure	– The neurological and systemic dysfunction is related to the site of tumor origin as well as child's age and developmental level – Neurological physical exam – Brain imaging – Referral to neurologist or neuro-oncologist
Leukemia and lymphoma [33]	
• Malaise, fatigue, pallor, anorexia • Fever without identifiable cause • Persistent/recurrent infections • Lymphadenopathy, hepatosplenomegaly • Petechiae, easy bruising • New limp when walking, bone pain (involving joints or generalized) • Neurological symptoms, irritability	– Physical exam with particular attention to integument, lymph nodes, abdomen (assessment of hepatosplenomegaly) – Referral to pediatric cancer center
Drugs and intoxication	
SSRI's [34, 35]	
• FDA Black Box warning: increased risk of suicidal ideations and behavior in patients under the age of 24 • Irritability, hypomania/mania in patients with undiagnosed bipolar disorder • Cognitive slowing, emotional flattening, apathy in some patients • Sexual dysfunction, insomnia, GI upset • Diaphoresis • Bruising, bleeding (rare) • Seizures (rare) • Serotonin Syndrome (increased risk with two or more serotonergic drugs)	– Dose-related side effects – Emotional flattening, apathy, and cognitive slowing from serotonergic effects upon CNS dopamine regulation – Serotonin Syndrome: classic triad of neuromuscular excitation (clonus, myoclonus, hyperreflexia, rigidity), autonomic excitation (hyperthermia, tachycardia), altered mental status (confusion, agitation). Obtain vital signs, labs (CK, Creatinine). Rule out ETOH withdrawal, substance use, non-convulsive seizures, encephalitis

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Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Alcohol [36, 37]	
• Family dysfunction, FHx of alcoholism, child's stress state, low behavioral self-control, age <20 and irritable, antisocial traits, sensation seeking behavior • Signs of ETOH withdrawal	– Screen for ETOH use including last drink, and change in amount – Vitals signs and physical exam with particular attention to evidence of autonomic hyperarousal – Serum ETOH level
Stimulants: Amphetamine and methylphenidate [38, 39]	
• Hypertension, tachycardia, palpitations, cardiac arrhythmias, tremor • Anorexia, weight loss, GI upset, xerostomia • Agitation, irritability, sleep disturbance • Psychosis • Peak and rebound effects, propensity for habit formation/substance use	– Peripheral side effects from norepinephrine (autonomic) and central side effects from norepinephrine and dopamine (psychosis, motoric effects, sleep disturbance, propensity for habit formation/substance abuse) – Vital signs, cardiovascular exam, ECG – Drug test
Caffeine [40–43]	
• Later bed times • Decreased sleep • Less sleep depth (reduced slow wave activity on sleep EEG) • Consumption of energy drinks may be correlated with increasing ADHD or Conduct Disorder symptoms	– Screen for caffeine consumption – No FDA daily caffeine limit for children (FDA is investigating the safety of caffeine in food products), but discourage caffeine consumption in children (American Academy of Pediatrics recommendations)
Steroids [44–46]	
• Mood swings, irritability, depression, mania, anxiety, psychosis • Children with family psychiatric history, autism spectrum disorder, acquired neurological deficits may be at higher risk	– Screen for anabolic steroid use – Rule out delirium – Consider short-term use of benzodiazepine – Consider low-dose neuroleptic – Consider SSRI
Atomoxetine [47–49]	
• Intellectual disability, developmental disability (Autism Spectrum Disorder) • Agitation, aggression, irritability, anxiety • Fatigue, decreased appetite, xerostomia, nausea, vomiting, dyspepsia • Increased blood pressure and/or heart rate	– Side effects are related to selective norepinephrine reuptake inhibition – Evaluate diet – Vital signs – Taper off
Cannabis [50–52]	
• Paranoia, insomnia, appetite changes • MJ cravings, tremor, perspiration, change in appetite, irritability, restlessness (cannabis withdrawal) • "New" MJ use following cannabis use	– Screen for substance use, specifically ask about cannabis use – 38% of adolescents with cannabis dependence use cannabis to avoid withdrawal symptoms

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Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Isotretinoin [53–55]	
• Development of depression • Development of suicidal thinking • Fatigue, poor concentration, forgetfulness • Irritability • Sadness, crying spells • Loss of motivation	– Chronological correlation of changes in mood with a course of isotretinoin acne treatment (mood alteration is variable but tends to occur later in treatment) – Discontinuation of the drug may result in rapid resolution of psychiatric symptoms (days to weeks)
Levetiracetam [56, 57]	
• Aggression, hostility, agitation, anxiety • Suicidal thoughts and acts • Sedation • Hematological abnormalities	– Side effects related to action on SV2A and other voltage gated/sensitive channels – Often has to be discontinued due to behavioral problems and sedation
Alpha 2 adrenergic receptor agonist (Clonidine) [58, 59]	
• Hypotension, dizziness, weakness, fatigue, headache, nervousness/agitation • Depression, insomnia • Nausea/vomiting • Has been associated with behavioral irritability	– Side effects related to action on alpha 2 receptors and imidazoline receptors – Adjust dose or taper off medication (careful attention to risk of rebound hypertension risk)
MDMA (ecstasy/molly) [60, 61]	
• Euphoria, energy, closeness to others • Irritability, aggression, impulsivity • Anxiety • Paranoia • Muscle cramps • Hyperthermia	– Screen for MDMA use/environments where it is commonly present (e.g., raves) – Screen for ETOH use – Screen for MJ use – Check electrolytes
Arterial/venous	
Migraines [62]	
• Headaches (often unilateral, throbbing) • Irritability • Decreased appetite • Fatigue • Depressive symptoms • Isolation	– Trigeminovascular projections from the medullary dorsal horn may target midbrain, hypothalamus, amygdala and basal forebrain, producing symptoms – Good history taking to rule out causes such as neoplasms, seizures, substance withdrawal – Neurological examination
Mechanical	
Post-concussion syndrome [63, 64]	
• Headache, fatigue, sleep disturbance • Dizziness • Frustration, irritability, depression • Forgetfulness, poor concentration • Nausea • Double vision	– Most PCS symptoms resolve within the first year – Irritability is one of the longest lasting symptoms among those presenting at about the onset of PCS – Neurological exam – Track cognitive symptoms

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Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Traumatic brain injury [65]	
• Personality and cognitive changes • Development of ADHD • Aggression, conduct problems, drug abuse • Anxiety, depression	– GCS score, length of post-traumatic amnesia, and duration of loss of consciousness in evaluating TBI severity – Neurological exam – Brain imaging
Infectious/inflammation	
Streptococcal infection [66–69]	
• Evidence of streptococcal infection • Development of OCD and/or Tic disorder • Pediatric onset • Motor hyperactivity • Choreiform movements • Abrupt onset of symptoms • "Sawtooth" clinical course pattern: abrupt onset, followed by quiescence, followed by abrupt exacerbation	– PANDAS is a clinical diagnosis – History (e.g., center criteria) – HEENT physical examination – Rapid antigen test for group A streptococci or throat culture, anti-streptolysin O titers (rise in antistreptococcal antibody within 4–6 weeks of symptom onset), anti-DNase B – Could consider repeat throat cultures during periods of wellness to rule out strep carrier state
Autoimmune epilepsy [70, 71]	
• New onset seizure activity • Mood changes • Psychosis	– Acute or subacute (<12 weeks onset of clinical symptoms) – Absence of evidence for: CNS infection, previous CNS disease, CNS tumor, trauma, toxic exposure, metabolic derangements – Evidence of well-defined clinical syndrome such as limbic encephalitis or NMDAR encephalitis – CSF inflammatory markers and/or evidence of inflammatory histological findings on biopsy – MRI findings (e.g., increased signal in mesial temporal lobe)
Nutrition	
Iron deficiency [72–77]	
• ADHD • Overweight • Restless Leg Syndrome • Poor PO intake • Diet low in meat and alternate foods • Menstruating female • Depends on the degree of deficiency and the rate at which the anemia develops. As the degree of anemia worsens: fatigue, exercise intolerance, tachycardia, cardiac dilatation, poor growth, and systolic murmurs may develop	– Iron is an essential cofactor in the production of dopamine and norepinephrine – Review diet – Consider dietician consult – If applicable, obtain a menstruation history – Iron studies (Ferritin should be included in the overall evaluation of children with ADHD) – Iron replacement with indicated and assessment for response
Copper deficiency [78]	
• Poor PO intake • Diet low in meat and alternate foods	– Copper is an essential cofactor in the production of dopamine and norepinephrine – Copper levels

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Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Zinc deficiency [78–82]	
• GI malabsorption, diarrhea • Eosinophilic esophagitis • Zinc deficient diet (e.g., diet high in starchy roots and tubers) • Minimal animal source protein • Diet with cereals and legumes high in phytates	– Zinc is an essential cofactor in the production of dopamine and norepinephrine – Review diet – Consider dietician consult – Zinc levels – Dietary changes vs. zinc supplementation
Cyanocobalamin deficiency (vitamin B12) [83]	
• Weakness, fatigue, anorexia • Irritability, personality change • Developmental delay/regression, poor school performance, memory loss • Paresthesias, paralysis, seizures • Vibratory and proprioceptive sense impairment, abnormal movements, ataxia • Anemia, macrocytosis, leukopenia • Glossitis on physical exam • Vomiting/diarrhea • Systolic flow murmur • Icterus	– Review diet – Consider dietician consultation – B12 level – Consider MMA
Magnesium [84]	
• Anxiety, panic attacks, "blocked breathing," "lump in the throat" • Depression • Headache • Insomnia • Dizziness	– Review diet – Consider dietician consult – Check Mg – Check Calcium – BMP (renal function)
Omega-3 fatty acid [85, 86]	
• History of preterm birth, history of decreased birthweight (~10% below average) • Auditory, visual language, reading, and learning difficulties • Serious illness, frequent coughs, colds, or accident in the past year • Polydipsia, polyuria	– Consider omega-3 fatty acid supplementation
Degenerative and neurologic	
Lead [14, 87–90]	
• Lethargy • Decreased activity • Anorexia • Intermittent abdominal pain • Constipation • Vomiting	– Screen for offending source: paint, dust, drinking water, cosmetics, soil, cookware, imported toys, parental occupations – Blood lead level – CBC w/ diff – Iron level – Abdominal radiography if ingestion suspected and bowel decontamination if indicated – Neurodevelopmental monitoring

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Table 3.1 (continued)

Mend A Mind Mnemonic	
Signs, symptoms, and risk factors	Workup
Alzheimer's dementia [91, 92]	
• Age greater than 65 years old • Family history of dementia • Memory impairment often the first presentation, declarative episodic memory impairment, semantic memory and immediate recall deficits • Executive function and problem solving impairment • Language and behavioral impairment later in the illness • Down's syndrome	– History, rule out other dementias: frontotemporal dementia, vascular dementia, Parkinson's, Lewy body – Physical examination – Rule out other causes of dementia: frontotemporal dementia, vascular dementia, Parkinson's, Lewy body – MOCA – CBC w/diff, CMP, TSH, B12 level – Brain imaging
Frontotemporal dementia [93, 94]	
• Personality changes • Changes in interpersonal conduct • Disinhibition • Stereotypic behaviors • Emotional dysregulation • Poor insight into symptoms	– History, rule out other dementias: Alzheimer's dementia, vascular dementia, Parkinson's, Lewy body – Physical examination – MOCA – CBC w/diff, CMP, TSH, B12 level – Brain imaging
Vascular dementia [95]	
• Stepwise decline in memory functioning • Cardiovascular history: HTN, heart disease, vascular equivalent (e.g., diabetes)	– History, rule out other dementias: Alzheimer's dementia, frontotemporal dementia, Parkinson's, Lewy body – Physical examination – MOCA – CBC w/diff, CMP, TSH, B12 level – Brain imaging
Mercury [96, 97]	
• Exposure from sources containing mercury such as fish • Another source of mercury exposure is dental amalgam. It has been suggested that dental amalgam does not cause neurobehavioral effects	– Identify exposure source – Mercury level – Assess for other heavy metal exposures
Organophosphates [98]	
• Exposure from sources containing organophosphates (e.g., food, drinking water, residential pesticide use) • Age 6–11	– Urinary metabolites of organophosphate pesticides

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