Anxiety and Anxiety Disorders

L. Jarrett Barnhill, MD, DFAPA, FAACAP

This section provides a brief overview of the adjunctive role for psychotropic drugs in the treatment of Anxiety Disorders in individuals with Intellectual and Developmental Disabilities (IDD) and Autism Spectrum Disorders (ASD). In this context, pharmacotherapy is part of a comprehensive treatment plan, not a stand-alone intervention.

From Anxiety to Anxiety Disorders

Anxiety represents a spectrum of emotional, somatic, and cognitive responses to both external and internal threats. The core features of anxiety arise from the basic neurobiology of fear (flight, fight, or freeze reactions) and fear-conditioned process that include generalization, sensitization, and resistance to extinction. At higher cortical levels, more complex neurocognitive processes generate anticipatory anxiety, agoraphobia, avoidance in response to perceived social disapproval, skill deficits in problem solving, intolerance of uncertainty, and anticipation of future threats.

Pathological anxiety is a step beyond developmental anxiety. It is anxiety that morphs out of the effects of trauma experiences, early loss, family chaos, and significant skill/problem solving deficits. Pathological anxiety usually presents as both internalizing and externalizing signs and symptoms that do not meet the full criteria for anxiety disorders. In at risk children, it may be a marker for prodromal or subsyndromal forms of anxiety disorders. An imbalance between genetic risk, life stressors and compromised resilience contribute to its progress towards full syndrome anxiety disorder.

The diagnosis of Anxiety Disorders (AD) requires meeting current diagnostic criteria. The DSM-5[1] and DM-ID-2[2] include Specific Phobias, Separation Anxiety, Selective Mutism, Panic, Social Anxiety, Agoraphobia, Generalized Anxiety, Specified and Unspecified Anxiety Disorders, as well as Anxiety Disorder due to Another Medical Disorder. Specific ADs are frequently comorbid multiple psychiatric disorders in which they accentuate their negative impact on quality of life, intensify emotional distress and suffering, contribute to secondary depression and complicate treatment outcomes.

ADs are the most common psychiatric disorders among individuals with IDD. The higher prevalence rates for anxiety reflect an imbalance between resilience, negative life experiences (including trauma) and other susceptibility factors. The prevalence rates for ADs are influenced by diagnostic uncertainty secondary to cognitive and communication deficits, misinterpretation of baseline exaggeration data, and diagnostic overshadowing. Severe/profound disabilities can also interfere with our ability to distinguish AD subtypes. For many with severe/profound IDD, Unspecified AD (overlapping trauma or adjustment disorder), AD due to Another Medical Disorder, and Generalized Anxiety Disorders are about as specific as can be determined.

Case Vignette

Phase 1: Interface between temperament, attachment, and separation anxiety and preventive interventions

AK was four at our initial contact. His parents were concerned about school avoidance in AK's first two weeks of pre-kindergarten. AK was described as a shy child with slow to warm up temperament, who rarely spoke outside the family setting. His past medical history revealed: premature birth at 32 weeks, significant intrauterine growth retardation, mild Cerebral Palsy (left side weakness) and Articulation Disorder. Early intelligence testing suggested borderline/mild ID. Family history was positive for Panic Disorder in Ms. K. and mild OCD in Dr. K. AK's 10-year old twin sisters were shy but doing well. On examination, AK revealed mild delays in most motor milestones, mild spastic left hemiplegia, mutism, and mild separation anxiety.

[1] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th ed.). Washington*, DC: American Psychiatric Association, 2013.

[2] Fletcher RJ, Barnhill J, Cooper S-A (Eds). *Diagnostic Manual-Intellectual Disability 2: A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability.* Kingston, NY: NADD Press; 2017.

AK's presentation illustrates the importance of an adaptive and stable family ecosystem in matching temperament, attachment needs, and enhanced resilience in early childhood disorders. It is also crucial to understanding the complex roles genetic risk, behavioral inhibition, articulation disorders, and neurodevelopmental problems can play in anxiety disorders. A positive family history of Panic Disorder and behavioral inhibition may contribute to separation anxiety, Selective Mutism and later onset anxiety and mood disorders.

AK responded to a brief exposure-graduated desensitization program and did not require pharmacotherapy. Pharmacotherapies are frequently required for children with severe anxiety, parental mental illness, disruptive family life, and chronic trauma and/or abuse. Older children and adolescents with Separation Anxiety may require intensive services for comorbid depressive-anxiety and/or externalizing disorders.

Phase 2. Interface between loss and grief, increasing anxiety, and a panic attack in a child vulnerable to Panic Disorder

The eighth grade presented new challenges for AK. First, his maternal grandfather died suddenly. AK lost his "best buddy." Then in rapid succession, AK had his first panic attack, an intensification of worries about dying and "not keeping up" at school.

During his assessment, AK described worries about his mother's sadness, his father's constant worrying, and missing his sisters, who entered college. His parents shared concern about AK reaching an academic ceiling secondary to his cognitive and learning disabilities and about his increased risk for depression.

A second issue arose from parental concerns about a recent onset of "night terrors." Their description was more consistent with nocturnal panic attacks (may affect 40% of individuals with Panic Disorder). His medical and neurological workups were negative. His neurologist ordered a polysomnography that did not support night terrors.

The mental status exam revealed relative anhedonia in conjunction with grief and growing anticipatory anxiety about another panic attack. The patient's therapist noted similar findings. Neither of us detected suicidal ideation or intent. CBT with modifications was started, but his symptoms persisted. At that point, his therapist, family and AK requested a trial of sertraline (his mother responded to it). Within eight weeks, he appeared euthymic and less anxious, but his sporadic nocturnal panic attacks persisted. We discussed adding clonazepam for night terrors but did not pursue it. AK did well. After two years on sertraline and CBT, we slowly tapered and discontinued his SSRI while continuing his modified CBT.

Phase 3: Interface between transitions, worry about many things, resurgence of panic attacks, and newly emergent seizure disorder

AK did well off sertraline until the beginning of his senior year. In May, his father called to report an intensification of his panic attacks and sleep episodes. When I saw AK, he described his anxiety in different terms. He described a "funny feeling" in his belly that "felt like a mouse running up chest" before his "scary spells." His parents and soccer coach noted that AK "had an odd look" then froze for a few seconds before he started fumbling with his clothes. The episodes ended with a period of confusion.

Clinically these ictal events resembled "complex partial seizures" intertwined with worsening anxiety. Valproic acid (VPA) was started and titrated up to a serum level of 85 mcg/d. Three months later, his neurologist concurred with the diagnosis of complex partial seizures and maintained VPA. He also wondered if his sleep disturbances also improved, suggesting nocturnal seizures. We increased his VPA and his seizures improved, but his panic attacks and depressed mood persisted. We restarted out-patient CBT and titrated his sertraline to 200 mg/d. His mood improved over the next 2 months.

Treatment: How Do We Help the Fly Get out of the Bottle?

This vignette reinforces two issues. First, the diagnosis and treatment of Anxiety Disorders requires a longitudinal, systemic/ecological perspective as clinical status may change over time. Secondly, the potential for diagnostic overshadowing of disorders can represent a two-way street, and that AD, neurodevelopmental, medical, and/or neurological disorders are not an either/or problem. Focusing exclusively on one or the other can backfire. These caveats support the concept that diagnoses are working hypotheses, not written in stone.

Current best practices trend toward Cognitive Behavior Therapy (CBT), Dialectical Behavior Therapy (DBT), Positive Psychology/Interactive Behavior Therapy (PP/IBT), exposure therapy, and other psychological interventions as preferred frontline treatments. Meta-analytic studies report similar response rates with frontline psychotropic medications (SSRIs and SNRIs). Combining therapies is a practical solution, but the evidence related to managing treatment non-responders suggests that this may be case-by-case decision. Despite this caveat, psycho/ecological therapies are useful for bracketing pharmacotherapies – used prior to assess need, and as a tool in reduction/elimination strategies as a means of relapse prevention.

Meta-analytic studies also suggest that psychotropic drugs can be organized into algorithmic hierarchies (see Table 1). Most pharmacotherapy algorithms begin with SSRI's and SNRI's as frontline treatments. Predictors of moving onto second, third and augmentation strategies usually boil down to a lack of response or intolerance. If the drug is not effective and diagnostic and pharmacokinetic parameters are not contributory, then interclass exchanges within Tier 1 and/or moving to the next tier, or augmentation is next. If a drug is not tolerated, then switching to alternative classes of medications is prudent.

The second and third treatment tiers are frequently older treatments or those without sufficient research support. As outlined in the table, there is a variety of drug classes and possible mechanisms of action in treatments; for example, older treatments (tricyclics, benzodiazepines) as a replacement for ineffective SSRI/SNRIs. The third-tier treatments are consistent with a high degree of variability within AD drugs like pregabalin, buspirone, beta blockers, multiple anticonvulsants and second-generation antipsychotics. They are usually Tier 3 interventions but can be preferentially effective in General Anxiety and Social Anxiety Disorders (performance specifier). The need for second and third tier treatments reinforces the biopsychosocial complexity of ADs in people with IDD.

Table 1. Categories of Anxiety Disorders

Category	**Anxiety Disorder**
Fear related	Panic disorder; Social Anxiety (performance); Specific Phobias; Separation Anxiety
Anxious anticipation of threat	Agoraphobia; Selective Mutism
Excessive worry and misery	Generalized Anxiety Disorders; Mood-Anxiety Disorders
Anxiety Disorder due to another medical condition, unspecified and anxiety/trauma anxieties may fall in each of the categories above.	

Table 2. Consensus Treatment Algorithm-Anxiety Disorders

Tier 1	• 1st and 2nd generation SSRIs and SNRIs • Short term benzodiazepines • Beta-blockers (social anxiety-performance related) ***Treatment non-responders:*** review diagnoses and current team-based treatment plan
Tier 2	• Pregabalin • Benzodiazepine and other GABA-Calcium channel mediating treatments • 3rd generation SSRI (Votioxine is most popular) • Tricyclic Antidepressants ***Treatment resistance:*** define tier level and comfort zone. Do not hesitate to seek second opinions/consults. It is useful to refer for a second opinion once.
Tier 3	• Reversible and standard MAO-A and B Inhibitors • Valproic acid and other anticonvulsants • 2nd and 3rd generation antipsychotic augmentation • Buspirone (Generalized anxiety) • Beta-blockers • TMS and somatic therapies • Alternative treatments

Summary

This review provided an overview of the role of pharmacotherapies as adjuncts in the treatment of AD in the context of IDD. SSRI's, SNRIs along with several psychotherapeutic interventions are generally front-line, trans-diagnostic treatments that are effective across the spectrum of anxiety disorders (including comorbid or externalizing variants).

However, there are exceptions. In general, "starting low and going slow" is the most sensible approach but even at "therapeutic ranges," prescribers can struggle with low remission, high relapse rates, and substantial numbers of non-responders to both psychotherapy and pharmacotherapies. One should remain cognizant that psychotropic drugs are adjunctive treatments, and that their true values lies in ecologically-based interventions.

References

Addington AM, Rapoport JL. Annual research review: Impact of advances in genetics in understanding developmental psychopathology. *J Child Psychol and Psychiatry.* 2012; 53: 510-518.

Allgulander C. Generalized anxiety disorder: Between now and the DSM-5. *Psychiatric Clin N Amer.* 2009; 32: 611-628.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th ed.).* Washington, DC: American Psychiatric Association, 2013.

Barnhill J, McNelis D. Overview of intellectual/developmental disabilities. *Focus.* 2012; X(3):300-307.

Barnhill J. Integrated pharmacological management. In Rubin IL, Merrick J, Greydanus DE, Patel DR. *Health Care for People with Intellectual and Developmental Disabilities Across the Lifespan.* Dordrecht, NY: Springer; 2016:601-1606.

Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: Developmental issues and implications for the DSM-5. *Psychiatric Clin N Amer.* 2009; 32: 483-540.

Caspi A, Moffitt TE. All for one and one for all: Mental disorders in one dimension. *Amer J Psychiatry.* 2018; 175(9):831-844.

Conn M (Ed). *Conn's Translational Neuroscience.* New York: Academic Press; 2017.

Cooper SA, Smiley E, Morrison J, Williamson A, Allan L. Mental ill-health in adults with intellectual disabilities: prevalence and associated factors. *Br J Psychiatry*. 2007; 190:27-37.

Cooper N, Feder A, Southwick SM, et al. Resilience and vulnerability to trauma: Psychobiological mechanisms. In Romer D and Walker EF (Eds). *Adolescent Psychopathology and the Developing Brain***.** New York: Oxford Univ Press: 2007; 347-372.

Davis E, Saeed SA, Antonacci DJ. Anxiety disorders in persons with developmental disorders: Empirically informed diagnosis and treatment. *Psychiatric Quarterly.* 2008; 79: 249-264.

Deutz MHF, Woltering S, Vossen HGM, Devotic M, van Baar AL, Orinzie P. Underlying psychophysiology of dysregulation: resting heart rate and heart rate reactivity in relation to childhood dysregulation. *J Amer Acad Child Adolescent Psychiatry.* 2019; 58(6):589-599.

Dilbanz N, Encz A, Cavus S. Social anxiety disorder. In Salek, S (Ed). *Different Views of Anxiety Disorders.* Rijeka Croatia: InTech: 2011.

Fletcher RJ, Barnhill J, Cooper S-A (Eds). *Diagnostic Manual-Intellectual Disability 2: A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability.* Kingston, NY: NADD Press; 2017.

Foa E. Commission on anxiety disorders. In Evans DL, Foa EB, Gur RE, et al (Eds). *Treating and Preventing Adolescent Mental Health Disorders: What we Know and What we Don't Know.* New York: Oxford Press; 2005.

Gonzalez P, Martinez KG. The role of stress and fear in the development of mental disorders. *Psychiatric Clin N Amer.* 2014; 37:535-546.

Harris JC. Advances in understanding behavioral phenotypes in neurogenetic syndromes. *Amer Med J Part C Sem Med Gen***.** 2010; 154(C):389-99.

Jorstad-Stein EC, Heimberg RG. Social phobia: An update on treatment. *Psychiatric Clin N Amer.* 2009; 32:641-664.

Kagan J, Snidman N. Temperament and biology. In Coch D, Fischer KW, Dawson G et al (Eds). *Learning and the Developing Brain.* New York: Guilford Press; 2007.

Katzman MA, Bleau P, Blier P, Chokka P, Amerigan MV. Canadian anxiety guidelines group. *BMC Psychiatry.* 2014; 14(suppl 1).

Kheirbek MA, Klemenhagen KC, Sahay A, Hen R. Neurogenesis and generalization: A new approach to stratify and treat anxiety disorders. *Nat Neuroscience.* 2012; 15:1613-1620.

Kreiser NL and White SW. Autism spectrum traits and recurring psychopathology: The moderating role of gender. *J Autism Dev Disab.* 2015; 45(12):3932-3938.

Kwok H, Cheung PWH. Co-morbidity of psychiatric disorder and medical illness in people with intellectual disability. *Curr Opin Psychiatry.* 2007; 20(5):443-447.

Lanouette NM, Stein MB. Advances in the management of treatment–resistant anxiety disorders. *Focus.* 2010; 8:501-524.

Lissek MA, Rabin S, Heller TE, Lukenbaugh D, Geraci M, Pine DS, et al. Overgeneralization of conditioned fear as a pathogenic marker for panic disorder. *Amer J Psychiatry.* 2010; 67:47-55.

Martin EI, Ressler KJ, Binder E, et al. The neurobiology of anxiety disorders: Brain imaging, genetics and psycho-endocrinology. *Psychiatric Clin N Amer.* 2009; 32:549-576.

Mangolini VI, Andrade LH, Latufo-Neto F, Wang Y-P. Treatment of anxiety disorders in clinical practice: A critical overview of recent systemic evidence. *Clinics.* 2019; 10:60-61

Matthew SJ, Price RB, Charney DS. Recent advances in the neurobiology of anxiety disorders: Implications for novel therapeutics. *Amer J Med Genetics.* 2008; 89-98.

Perez-Edgar K, Fox NA. Temperament and anxiety disorders. *Ch Adol Psychiatric Clin N Amer.* 2005; 14:681-706.

Reiss S. *The Concept of Anxiety Sensitivity: Possible Implications for Research on Dual Diagnosis.* Kingston NY: NADD Press; 2000.

Royall College of Psychiatrists. *Diagnostic Criteria for Psychiatric Disorders for Use in Adults with Learning Disabilities/Mental Retardation.* London: Gaskell; 2001.

Rutter M. The interplay of nature, nurture and developmental influences: The challenge ahead for mental health. *Arch Gen Psychiatry.* 2002; 59(11):996-1001.