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CHILD AND ADOLESCENT PSYCHIATRIC CLINICS

Strategies for pharmacologic treatment of high functioning autism and Asperger syndrome

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This article discusses strategies that assist in medication treatment of individuals with Asperger syndrome (AS) and high functioning autism (HFA). Elsewhere, there are recent reviews offering detailed information on medications used for HFA and AS [1]. The objective here is to discuss the logic and organization of medication treatments for symptoms of HFA/AS and ways to decide which medications may be useful.

AS and HFA have moved from being esoteric, ''boutique'' conditions into the mainstream of child and adolescent psychiatric practice. Diligent practitioners recognize they must be informed about the diagnosis, course, and treatment of these disorders. Recent epidemiologic studies suggest a prevalence of approximately 19–67/10,000 individuals for autism spectrum disorders [2–4]. Moreover, autism spectrum disorders are no longer the exclusive province of specialists. A typical child and adolescent psychiatric practice is likely to see patients from the roughly 50%–60% of the PDD population who are ''high functioning,'' that is, they have good functional semantic language skills and average or greater IQ. Many individuals with these disorders have mood and behavioral problems [5], and moderate to severe symptoms certainly lead parents to seek treatment with a child and adolescent psychiatrist. Reports from education departments suggest students with these conditions represent a large influx of new special education students [6] and place a heavy demand on education systems.

Although there has been an effort to identify features that differentiate HFA and some AS [7,8], it is premature to be confident about this distinction [9–12].

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Specifically, longitudinal studies have not demonstrated differences in prognosis [9,13]; it is possible that the outcome can overlap [11]. There is no evidence that the groups show a different response to interventions for social skills development or that there are differences in basic information processing [14–18]. Furthermore, there is no evidence that the two disorders exhibit genetic specificity or different recurrence risks. There are no differences in neuropathology that have been demonstrated [19]. This discussion therefore considers both "high functioning" groups together under the designation HFA/AS. For the purposes of pharmacologic treatment this is particularly justifiable because no studies have reported differences in medication responses in those persons with HFA compared with those with AS.

Core features and the mechanics of pharmacologic treatment

It is essential for anyone who takes responsibility for pharmacologic treatment to understand the phenomenology and course of HFA/AS (discussed elsewhere in this issue). The specific features of HFA/AS exhibited by a patient influence the treatment one chooses and how the treatment is assisted for that patient (and family). The nature of HFA/AS introduces specific and sizable challenges, particularly when using pharmacologic treatments. Building a relationship and gaining the patient's trust can be hard to accomplish; patients often feel forced to take medication and commonly recoil from the idea of medication treatment. Understandably, many patients are so frightened of the effects of medications that they cannot put those fears aside enough to try one. The amount of anxiety that makes it appropriate to consider medication for a patient can also interfere with him or her adhering to a prescription. Despite the enormous interference or distress their symptoms generate, many patients cannot put aside their worries about the medication. The family and a trusted physician may be the only people the patient will allow to counter these fears. Usually, creating a therapeutic framework for medication treatment that achieves this rapport requires time and several visits [20].

Many of the difficulties with anger, perseveration, or anxiety are more distressing to those around the patient than to the patient himself (or herself). Persons with HFA/AS commonly lack the ability to perceive the signals of comfort or pleasure of others or, once acquired, to use others' emotions to guide their behaviors. Lacking this ability, patients struggle with the initial fears related to taking medication or entering into other therapy that might help them get along with others. Often they cannot see why they should be required to take a medication simply because others are upset. Threatening an unpleasant consequence is often ineffective. Persons with HFA/AS can be willing to accept dreadful consequences rather than yield control to someone else, compromise a rigidly held rule, contain a pressing urge, or tackle managing an anxious feeling.

Another hurdle is the shortcomings patients have in identifying their own internal mood states and emotions. As a result, the clinician may be unable to gauge whether patients experience less subjective anxiety, sadness, or anger. The

patient's psychological "comfort" may not be available to the clinician for rating improvement. To monitor progress, the clinician is compelled to draw on multiple observations, rely more or less exclusively on the patient's somatic experience, and to use highly concrete measures with patients. Treating adult patients who are living independently and are unwilling to allow others to participate in their treatment is particularly challenging.

An associated obstacle is the deficits HFA/AS persons have perceiving and understanding other people's intentions, wishes, or needs. The blindness to others often contributes to the HFA/AS person's inability to grasp how their reactions contributed to a bad result; more often they believe they are being persecuted. The bona fide teasing and persecution that are a common part of their day-to-day experience only adds to this. For the person with HFA/AS, it may be impossible to tell the difference. Nevertheless, the person with HFA/AS is likely to be oblivious to how their actions contributed to a chain of events that ended in an outburst or aggression, or even to believe that the outcome should be averted in the future. This blindness also produces a tendency to accuse those around them of causing problems; faulting others is highly characteristic and is a direct result of the primary disorder. This should not to be confused with the more common psychological defenses of avoiding responsibility and assigning blame that are used by more socially skillful, typical agemates.

Many individuals with HFA/AS display profound weaknesses in the ability to observe sequences of events and transactions accurately and in understanding the "logical" responses of those around them. HFA/AS children can be highly concrete; the "big picture" of behaviors and emotions is often lost to an excessive attention to small changes in circumstances or minor details. They often have a flawed sense of proportion. For example, premeditated, forceful, retaliation may be viewed as a justified response to someone else's small blunder.

In addition, HFA/AS persons often are rigid in their behaviors with inflexible routines, dedication to unnecessary rules, or ritualized behaviors. Sometimes these may be no more than a minor irritation to others, but when severe, they can obstruct action and exasperate those around them. Severe rigidity can be highly frustrating to others, and attempts to counter it may produce aggressive reactions from the patient. For all this, such patients may perceive that "if only people let me do what I want" there would be no problems at all. HFA/AS patients are not merely immature ordinary children or adolescents.

In addition to these, several other obstacles are related to the state of the field. First, no pharmacologic agent influences the core pragmatic social deficits such as misinterpreting cues or failure to appreciate social cues and nuances. As a result, there is no one algorithm to follow that targets the primary source of impairment or the greatest source of difficulty for the patient. Second, there is an absence of high quality, valid studies of the efficacy of different pharmacologic agents for specific symptoms in this population. Most of the studies are case reports or small-scale, open, unblinded trials [1]. This requires the clinician to take findings from studies of other disorders in the hope that the results translate to HFA/AS. This presumption is entirely theoretic at this point. Much of the time, a clinician has

no way to gauge the patient's response in comparison with other individuals with this condition; global functioning may or may not be meaningfully improved. A third obstacle is the absence of treatment and outcome studies of HFA/AS with comorbid conditions. For example, it may be erroneous to presume that mood dysregulation and the response to mood stabilizers in the context of HFA/AS is identical to bipolar disorder in an otherwise ordinary adolescent. Nearly all treatment studies of other childhood disorders exclude persons with PDD spectrum disorders. Consequently, when a patient appears in the clinician's consulting room, unless one has the luxury of a previous relationship and sense of that patient's baseline functioning, one cannot know what the individual looks like when the comorbid condition is "resolved." Most of the core social impairments are likely to remain, although functional gains are possible.

Treatment strategies

In response to these challenges, there are strategies that clinicians can adopt that increase their chance of success. A prominent characteristic of the care of people with HFA/AS is the need for clinicians to integrate behavioral and pharmacologic treatments [21]. Thus, treatment strategies must embrace nonpharmacologic and pharmacologic interventions. The strategies shared by both interventions are genuinely complementary. Behavioral and pharmacologic care must establish realistic expectations, optimize the home and school (or work) environment, implement strong parental collaboration, and focus on specific symptom clusters.

It is most important to establish realistic expectations about the effect of medication (and other treatments). Many people are drawn to pharmacologic treatment with the expectation that the response will be rapid and complete. Excessively positive expectations may be intrinsic to HFA/AS, but they also can be related to the anxiety that one is hoping to alleviate. In any case, anxious HFA/AS patients often are unable to cope with the constraints that treatments are imperfect and require time. Even for people with more common disorders, rigidly holding to over-optimistic expectations can undermine treatment under the best of circumstances. For people with HFA/AS, having such expectations may be exceptionally likely. More than others, persons with HFA/AS may require the relief that comes from things being predictable and uncomplicated. They may be highly anxious about treatments that take time and give mixed results. For persons with HFA/AS more than others, achieving a different outcome from the one that was anticipated may be harder to endure. Many patients also have the mistaken idea that their symptoms will remit more quickly with pharmacologic treatment than with behavioral psychotherapies. It is therefore important for the clinician and the patient to understand that there are no "magic bullets," nor any "quick fixes" when it comes to treating these symptoms.

Individuals with HFA/AS also may be more prone to side effects. Typical children and adolescents may experience these as more of a nuisance than a source of major impairment, but persons with HFA/AS often find even minor side

effects hard to tolerate. The exquisite and atypical sensory world of individuals with HFA/AS means that they may experience a greater variety and rate of these kinds of side effects. When side effects appear, they often outstrip the patient's ability to follow conventional advice "to just ignore it." We do not know if the actual amount of discomfort is greater or if the means for self-soothing, distraction, or rationalization are insubstantial. In either case, some HFA/AS individuals cannot tolerate some medications because of "minor" side effects that patients who do not have HFA/AS handle with relative ease. In addition, they may be less likely to report side effects, or may allude to them in a manner that makes it much harder to detect them. Clinicians may be misled by comments that are offered in a flat, toneless manner, suggesting minor uneasiness for the patient when in fact they are extremely distressing. Similarly, highly concrete patients may not report side effects because the clinician does not ask about each specific one. Some patients stop their medication without telling the clinician in order to extricate themselves from the discomfort of side effects or having to talk about them.

Although clinicians frequently believe environmental and educational interventions can be helpful, physicians often rely on medication. This may be the request of the patient and others in his or her life, but it may not serve the patient in all circumstances.

A large 15-year-old youth with HFA attending a day school program displayed average receptive language but weak expressive language abilities. He was referred with the expressed request to increase the dose of his neuroleptic medication after showing increased agitation, irritability, and physical behavior at school. It seemed that these behaviors increased sharply over 3 weeks. He had been sent home several times in the last month following noncompliance with requests, outbursts of anger, and knocking over furniture. When asked, program staff did not remark on any precipitants. The patient's parents reported an increase in anxiety at home. Discussion with the patient's parents revealed that this young man had been expressing concerns over an impending labor strike at his program. He had reiterated, in an echoic way, conversations occurring in his presence among staff about the prospects for abrupt cessation of the program. At home he was tearful, apologetic, and anxious. Staff members at the program were unaware that he grasped their remarks or that the comments might influence him. When they explained that he would be given advance warning of any changes and he would continue to receive services in other ways, his agitation, outbursts, and irritability ended.

Thus, pharmacotherapy certainly has a place in an overall treatment plan, but physicians must be particularly mindful that *educational and behavioral supports are the mainstays of treatment for these conditions*. Medication can augment services, but when educational and other services are inadequate or unavailable, pharmacotherapy cannot make up the difference. Similarly, acute behavior changes usually should lead one to implement educational and behavioral supports that may be helpful before adding pharmacotherapy, except in uncommon circumstances that are discussed in detail later.

Parental collaboration is necessary to accomplish adequate medication treatment for HFA/AS. This goes well beyond helping a patient make the necessary

changes in his daily routine that taking a medication imposes and assuring his adherence to a medication regimen. The nature of HFA/AS itself places additional demands on parents and caretakers to participate in the treatment. Most patients with HFA/AS are weak intrinsically in their abilities to perceive their actions or feelings, recall them accurately, compare them at one time with another time, or observe a pattern of emotional or behavioral responses to events or a context. Children and adolescents with HFA/AS, to a greater extent than typical children and adolescents, cannot grasp or respond to the intentions, needs, and desires of others. At an elemental level, they have only a modest awareness of the difficulties their symptoms create for themselves and those around them.

Thus, parents play a crucial role in monitoring the patient by providing information to the physician, administering medication, observing for side effects, and noting behavioral and emotional effects. On the one hand, clinicians might imagine that medication treatment for children with HFA/AS might be simpler if one chose to meet with only a parent. Safe use of these medications requires that the patient inform his or her doctor about side effects, however, and have the chance to voice any worries he or she harbors. It is equally true that children with HFA/AS tend to be self-centered and limited in their focus, which undermines the value of their subjective reports of overall functioning and improvement. As a result, objective reports of behavior, mood, and general functioning are needed. Taken altogether, a vital objective of the treatment relationship is gaining a sturdy, reliable, comfortable, knowledgeable collaboration with the patients' parents and with the patients.

All HFA/AS treatment is only relatively specific now. This will be so until research identifies the specific neurochemical or genetic defects that produce HFA/AS and discovers a biologic or behavioral treatment that targets those defects. To make treatment specific, the psychopharmacologist cannot merely prescribe whatever is new or untested. Decisions about which agents to use should be based on what is likely to be most helpful for the individual patient's symptoms. A *symptom-focused method* means that the clinician is seeking the patterns of behavior in his or her specific patient with HFA/AS that are creating obstacles to optimal educational and social experiences. It is an imperfect process and forces clinicians to assess what can be achieved with educational and behavioral treatments, and to be knowledgeable about what symptoms medications are capable of ameliorating. The clinician's goal is a reduction in the *specific* symptoms that interfere with functioning. It is extremely unlikely that current medications will increase skills, but they may reduce the interference a patient experiences and allow him to use the skills he possesses.

Establishing treatment priorities

The quantity, scale, and range of difficulties experienced by HFA/AS individuals can be perplexing. Everyone involved, the patient, family, and clinician, can be swept up in this complexity. The first challenge is to create the hierarchy of

Box 1. Considerations for establishing treatment priorities

1. Symptoms that threaten the safety of patient, family members, or others
2. Symptoms that generate subjective distress for the patient
3. Symptoms that are sources of adversity in the family's life
4. Symptoms that jeopardize sustained educational progress

symptoms and the problems they create. Often, difficulties fall into a cluster of symptoms. The primary task of the clinician is to determine which symptoms should be targeted first. Box 1 suggests the questions and order of consideration when approaching this quandary. Although no clinical trials have used combined approaches, it is likely that combined modalities will be a part of the child's care outside the consulting room. Creating a hierarchy of specific symptoms lends itself to behavioral and pharmacologic modalities. In coordinating services, simultaneously directing behavioral and pharmacologic treatments to the same symptoms may well enhance the response.

Safety is the most compelling reason that HFA/AS patients are referred for pharmacotherapy. Aggression and violent outbursts are common in persons with HFA/AS [22,23], and individuals with HFA/AS commonly engage in other types of dangerous behaviors such as throwing or destroying objects [23]. Moreover, there are features of the disorder that make aggression and self-injury harder to control. Among other reasons, deficits in abilities to soothe and comfort themselves, the comparative insignificance of others' distress, rigid adherence to patterns or behaviors, deficits in generalizing from one circumstance to another, and the tendency to engage in repetitive and stereotyped behaviors may contribute to this intractability. As a result, the safety to patients and those around them are the highest priority.

A patient's subjective distress takes center stage once safety is not a primary worry. Relief of suffering in itself is a worthy objective, but focusing on the distress of HFA/AS patients goes beyond this generic physician mandate. HFA/AS patients who are sad, anxious, or continually irritable are thwarted in their ability to learn, monitor themselves, and "read" their environment. Their emotions override their abilities to perceive events and think through the solutions to everyday problems; they cannot respond with the necessary flexibility to the rapidly changing demands of the social world. As a result, subjective distress closes off opportunities to learn information, increase social relating, and gain new social skills. A patient in continual distress is likely to be unable to demonstrate his or her actual abilities.

The effects of an HFA/AS child's symptoms on a family are diverse, and some symptoms can be exceptionally taxing. Adverse effects on a family can be difficult to isolate and harder still to quantify. (Volumes could be written on the effect of HFA/AS on families.) Clearly, some symptoms exhibited by HFA/AS

children exceed what families can manage and may jeopardize a child remaining at home. Symptoms that imperil a child living at home deserve the most strenuous efforts to avert institutional or foster placements. The way a family adapts to a child with HFA/AS grows out of a complex interplay of the child's constitutional factors, such as his skills, deficits, and temperament, and the measure of limitations and demands of other family members that must be met. Cultural influences and community responses also can have a potent moderating or amplifying effect. Certainly the way parents and siblings adapt to a child's limitations and demands is a factor in the child's overall adaptation. The clinician may be required to decide which contributions to an adverse family environment warrant family treatment, couples treatment, or further psychoeducational interventions, and which are likely to benefit from pharmacotherapy. A common misjudgment is using medications to treat the patient's symptoms when a parent's depression or anxiety is a major contribution to family strain. Frequently, high levels of parental distress lead clinicians to prescribe for the child rather than educate parents and recommend that they obtain treatment. This is not to advocate that family members must be infinitely adaptable to impairing symptoms in a child or that family problems are always the result of parental disorders. The point is that family distress has many sources. Using medication may reduce a patient's inflexibility, instability, and anxiety, and thereby enhance life at home for everyone. If the relentless stress of raising a child with HFA/AS has fueled depression or an anxiety disorder in a parent, or inflamed conflicts in a marriage, however, usually treating only the child is insufficient. To treat clinical disorders in a parent or the tensions between partners, it is most likely that specific treatment is needed.

Similar to the risk for being unable to continue living at home, some behaviors can jeopardize a good educational placement. For example, when minor daily schedule changes lead a child to display aggression, withdrawal, or severe tantrums, if the school placement is at risk then there may be a role for medication to supplement vigorous behavioral efforts. This is particularly relevant when the program previously met a child's needs and then no longer is able to because of increasing symptoms or new symptoms that programmatic changes cannot reduce. On the other hand, not every program is ideal for every student. Some school placements do not fit the child's needs well and on occasion there are requests for medication that are based on a misunderstanding of the patient and his or her disorder. Medication should not be used to force a fit to a school program that poorly matches a patient's needs. Discussions with teachers, parents, special education administrators, and autism resource staff at the school often are necessary to sort out important medication decisions.

Characterizing symptoms

Behavioral and pharmacologic treatments of HFA/AS share a basic principle—a detailed characterization of the specific symptoms is needed to select the

proper intervention. In part this is an outgrowth of the integration of behavioral and pharmacologic approaches. However, even if the integration of behavioral supports and biologic interventions were not necessary, these symptom details would be needed. A careful analysis of symptoms is important because the choice of interventions is influenced by symptom characteristics. Furthermore, the wide array of symptoms engenders an inclination of those closest to the child to lose sight, over time, of the intervention targets. When observers turn their attention to a new troubling cluster of symptoms, a treatment that has been effective may be reinterpreted as ineffective. Being attentive to symptom characteristics permits the clinician to measure effects and introduce thoughtful responses. The most important characteristics to consider are shown in Box 2.

The distribution of behaviors is a term for the frequency of symptoms over time. It may be self-evident, but it is worth underscoring that for most people, the frequency of symptoms changes within days, weeks, and months. Thus, having a good awareness of the course of a symptom is important for monitoring medication effects. The early, short-term effects of a medication may not be the most reliable ones for predicting the overall effect that medication delivers. Frequency also usually is related to settings and circumstances. Aggression or perseverative behaviors often increase or emerge under certain circumstances, such as when there are many people talking or when there are crowds. Consequently, for behaviors that are episodic it is useful to rate the behavior at the time when it is most frequent or likely to surface, rather than a general rating throughout the day, week, or month. Furthermore, when symptoms are concentrated to specific times or places, one should first consider behavioral or educational interventions carefully. It may be that greater direction for certain activities, a break from interaction, or modifying the expectations for the patient in an activity will go a long way toward reducing maladaptive behaviors. Similarly, the risk for side effects should match the frequency of a behavior. If a symptom arises rarely, then it does not make sense to use an agent that carries a high risk for serious side effects or is highly likely to produce side effects that have the potential to make the patient uncomfortable.

Intensity is a measure of the energy or concentration the patient uses when engaging in the behavior. It also can be helpful to base this rating on the ease with which a patient may be redirected to another, different line of behavior. The onset

Box 2. Characteristics of symptoms

1. Distribution
2. Intensity
3. Onset: Time and Location
4. Duration
5. Ameliorating Factors
6. Aggravating Factors
7. Trends: upward or downward

of symptoms is often related to a time and a location. The ability to know when and where symptoms surface, or under what circumstances they surface, is helpful in rating progress. In addition, if a symptom only arises in one setting then this might lead one to consider intensive behavioral interventions first. More generalized behaviors might lend themselves more to pharmacologic treatments, because it can be difficult to maintain uniform responses across many different settings for behavioral interventions. Duration is self-explanatory. Aggravating and ameliorating factors can indicate what triggers a behavior or what sustains it.

The reason to consider the trend of a behavior, that is, whether it is increasing or decreasing, is that an intervention that is introduced as a behavior is winding down may be wrongly considered as having helped. Often, patients or their families seek treatment when a behavior is peaking in severity. For episodic conditions, by the time a clinician intervenes, the behavior may be cycling down by itself. It is therefore often helpful to wait before intervening, to learn about the pattern and characteristics of a behavior. Of course, this cannot be considered when the risks to safety or jeopardy to other aspects of the patient's wellbeing prevent the clinician from taking this time. If there is some doubt about whether symptoms may respond to behavioral treatment, or if one is unsure whether things have improved or remained the same, a clinician is advised to wait. Increasing doses or starting new medications should only go forward if one is sure that symptoms are worse or improved to a small degree.

A 12-year-old boy with AS was brought to treatment for picking and scratching behaviors that had become a part of his nighttime routine before going to bed. Each night he would scratch or dig at his legs. After extensive efforts to learn about the pattern of his behaviors, it seemed that these behaviors were influenced by the course of interactions at school during the day. Although the patient himself did not make the connection between being teased or having disagreements with classmates and his self-picking, it was possible to use medication and relaxation techniques to reduce the intensity and duration of these behaviors. In addition, the patient's parents were able to talk with him in the early evening about specific events from throughout the day that might create distress before he went to bed. Over time the behaviors were significantly reduced, although they did not disappear altogether.

Deciding on modality priorities

The integration of behavioral and pharmacologic treatment can place clinicians in the predicament of deciding whether to pursue behavioral or pharmacologic treatment. There are patient and symptom characteristics that should enter the equation. Patients who work hard with a behavioral support system are obviously ones who should be treated vigorously in this manner. Other patients resist behavioral work or have circumstances that do not lend themselves to behavioral treatments. For example, it may be difficult to use behavioral treatments at home with frail caretakers who may be physically intimidated during attempts to ignore

maladaptive behaviors. As indicated earlier, there are some scenarios in which the clinician might request a more thorough application of behavioral treatment before engaging in pharmacotherapy. The features that indicate vigorous behavioral treatment are those that are more infrequent, highly setting- or circumstance-specific, and moderately (or less) intense. It is important to consider whether behavioral treatments have been conducted properly, were of sufficient duration, and were provided with sufficient intensity. A history of well conducted but unsuccessful behavioral treatments suggests that one should move to medication along with behavioral supports.

Six symptom clusters

For simplicity, six clusters of symptoms are discussed. Throughout this discussion the emphasis has been on specific symptoms and this is an important feature to emphasize. If a patient repetitively seeks elastic objects to stretch and chew, then that symptom is the one to be targeted; for this discussion it would fall into repetitive behaviors and inflexibility. The monitoring of that symptom, however, means that the clinician and others are all tracking perseverative behavior with elastic—not every repetitive behavior that the patient may display. The clusters that follow are only a convenient way of talking about pharmacologic treatments for the common kinds of behaviors that impede the lives of people who have HFA/AS. These clusters are hardly comprehensive and there certainly could be more. These were chosen because they are common reasons to seek pharmacotherapy for persons with HFA/AS.

Aggression

Aggression is seldom an isolated problem and is particularly complex in individuals with HFA/AS [23]. It is important to understand that aggressive behavior is not always associated with just one condition and can have highly varied sources. An array of theoretic models has been proposed to understand aggressive behavior in persons with HFA/AS [24]. There are promising biologic models that suggest the behavior arises from alterations in dopaminergic reward mechanisms [25], and cognitive models, suggesting that such acts are an outcome of conditioned learning [26,27]. Tantrums and physical aggression are often responses to a variety of circumstances and occur in the context of diverse emotions [23]. It has become fashionable to consider aggression as prima facie evidence of bipolar disorder, particularly when HFA/AS individuals are distractible, restless, and have chronically decreased need for sleep. It is increasingly important to consider, however, whether features of bipolar illness appear together and depart from chronic baseline functioning. It is also relevant if they are associated with pharmacologic (eg, serotonin reuptake inhibitor) side effects. It is useful to know the circumstances preceding and following aggressive outbursts before selecting a pharmacologic agent. For example, when aggression is a response to anxiety or frustration, the most helpful interventions target those

symptoms and the circumstances that produce them rather than exclusively focusing on aggressive behavior. Unfortunately, the request for treatment typically follows a crisis and the press for a rapid, effective end to the behaviors may not permit the gathering of much data or discussion. Nevertheless, it is not appropriate to "always" begin with one agent or another. Moving to a more "surefire" agent too quickly may mean that the patient takes on cardiovascular, endocrinologic, and cognitive risks that might be otherwise avoided. There are reports in support of using serotonin reuptake inhibitors (SRIs) [28–34] (Table 1), alpha-adrenergic agonists [35] (Table 2), beta-blocking agents [36,37] (Table 3), "mood stabilizers," (or anticonvulsants) [38] (Table 3), and neuroleptics [39–45] (Table 4) for aggressive behavior. When a clinician has the luxury of time, the support of family, and collaboration with staff where the individual is working or attending school (or living), then an agent that is safer, but perhaps takes a longer time to work or is a little less likely to help, can be tried. It does seem that those agents with a greater likelihood of success pose greater risks [22,46]. The most evidence supports use of dopamine blocking agents (neuroleptics) for aggression [22] (Table 4), but the side effects and long-term risks from these agents are greater than others listed earlier.

Anxiety

Individuals with HFA/AS are particularly vulnerable to anxiety [47,48]. This vulnerability may be an intrinsic feature of HFA/AS [49] through specific neurotransmitter system defects [50], a breakdown in circuitry related to extinguishing fear responses [51], or a secondary consequence of their inability to make social judgments [15–17] throughout development. The social limitations of

Table 1
Serotonin reuptake inhibitors

Generic medication	Brand name	Dose range	Comments
Clomipramine	Anafranil	25–250 mg/d	Sedating. Highly anticholinergic, requires ECG monitoring.
Citalopram	Celexa	10–60 mg/d	Range of side effect severity. Insomnia,
Fluoxetine	Prozac	5–120 mg/d	sedation, mild GI upset, loss of
Fluvoxamine	Luvox	12.5–300 mg/d	appetite, activation.
Paroxetine	Paxil	5–50 mg/d	Drug–drug interactions require care
Sertraline	Zoloft	12.5–200 mg/d	when combining other medications, especially dopamine anatagonists.
Trazodone	Deseryl	25–600 mg	Highly sedating
Mirtazapine	Remeron	5–45 mg/d	Noradrenergic in addition to serotonergic properties. Very different side effect profile: agranulocytosis risk, hypertension, weight gain, cholesterol elevation, in addition to above. Open trial showed only modest effects.

Table 2
Alpha adrenergic agonists

Generic medication	Brand name	Dose range	Comments
Clonidine	Catapres	0.1–0.3 mg/d	ECG before starting. Sedation and hypotension are most common side effects. Divided doses are critical.
Guanfacine	Tenex	0.5–2 mg/d	

HFA/AS make it difficult for individuals with the disorder to develop coping strategies for soothing themselves and containing difficult emotions. Limitations in their ability to grasp social cues and their highly rigid style act in concert to create repeated social errors. They are frequently victimized and teased by their peers and cannot mount effective socially adaptive responses. Limitations in generalizing from one situation to another also may contribute to repeating the same social gaffs. Furthermore, the lack of empathy severely limits skills for autonomous social problem solving. For higher functioning individuals, there is sufficient grasp of situations to recognize that others "get it" when they do not.

Table 3
Other agents

Generic medication	Brand name	Dose range	Comments
Opioid antagonists			
Naltrexone	Revea	1 mg/kg/d	Few adverse effects. Little benefit for self-injury.
Serotonin agonist			
Buspirone	Buspar	5–45 mg/d	Watch for possible akathisia-like reaction, sedation.
Benzodiazepines			
Clonazepam	Klonopin	0.25–2 mgs	Sedation, paradoxical agitation, emotional blunting. Ataxia at high doses. Discontinue gradually after chronic use.
Lorazepam	Ativan	0.5–2 mgs	
Beta-blocking adrenergic agents			
Naldolol	Corgard	20–220 mg/d	Hypotension, bradycardia require close attention. BID dosing is preferred.
Propranlol	Inderal	10–120 mg/d	
Pindolol	Visken	5–30 mg/d	Hypotension, bradycardia. BID or TID divided doses are recommended. Has some 5-HT activity, too.
Anti-convulsant/Mood Stabilizers			
Carbamazepine	Tegretol		Beware: aplastic anemia, agranulocytosis, hepatotoxicity, cardiac changes, sedation. Blood level monitoring essential.
Divalproex	Depakote		Beware: hepatic failure. Thrombocytopenia, nausea, sedation, headache, GI disturbances, tremor, dizziness. Blood level monitoring essential.

Table 4
Dopamine antagonists[a]

Generic medication	Brand name	Dose range	Comments
Haloperidol	Haldol	0.25–10 mg/d	Parkinsonian side effects, probable greater TD risk
Olanzapine	Zyprexa	2.5 QOD–20 mg/d	Significant weight gain, diabetes mellitus, QTc prolongation. Anticholinergic effects at higher doses. TD risk
Quetiapine	Seroquel	50–350 mg/d	QTc prolonged, orthostatic hypotension, tachycardia, weight gain, seizure risk, thyroid effects, possible cataract risks, TD risks.
Risperidone	Risperdal	0.5–6 mg	Orthostatic hypotension, sedation, weight gain, QTc prolongation, TD risks, dose-dependent Parkinsonian side effects.
Thioridazine	Mellaril	10–500 mg	Heavy anticholinergic side effects, sedation, probable greater TD risk, QTc prolongation
Ziprasidone	Geodon	10–120 mg/d	Significant risk of QTc prolongation, sedation, rash, TD risks, possible lower risk of weight gain among atypical agents.

[a] See refs [85, 86]

For others there is only the discomfort that comes from somatic responses that are disconnected from events and experience.

Several agents have been tried for treatment of anxiety. There is no reason to suspect that individuals with HFA/AS are less likely to respond to the medications used for anxiety in persons without HFA/AS. Thus, SRIs [28–34,52] (Table 1), buspirone [53] (Table 3), and alpha-adrenergic agonist medications such as clonidine or guanfacine all have been tried [35] (Table 2). The best evidence to date supports use of selective serotonin reuptake inhibitors (Table 1). It is also true that individuals with HFA/AS may be more vulnerable to side effects and to exhibit unusual side effects. Disinhibition is particularly prominent and can be seen with any of the serotonin reuptake inhibitors; in some circles this is regarded as evidence of bipolar ''switching,'' although there are no studies to suggest that among persons with HFA/AS this reaction is a portent of later nonmedication-related mania. Similarly, excessive doses may produce an amotivational syndrome [54].

Depression

Depression seems to be common among HFA/AS individuals in adolescence and adulthood [55]. Many of the same deficits that produce anxiety may conspire to generate depression. The relationship between serotonin functioning and depression has been explored in detail [56–59]. There is also good evidence that serotonin functions may be impaired in persons with HFA/AS [60] and which suggest that depression and HFA/AS would be more likely. Another possibility is that the basic circuitry related to frontal lobe functions in depression may be affected in persons with HFA/AS [61]. In addition, deficits in social relationships and responses that

permit one to compensate for disappointment and frustration may fuel a vulnerability to depression [15–17,55]. There is some genetic evidence suggesting that depression and social anxiety are more common among first-degree relatives of autistic individuals [62], even when accounting for the subsequent effects of stress.

The medications that are useful for depression in typical children and adolescents should be considered for individuals with HFA/AS who display symptoms of depression. It exceeds the scope of this discussion to detail the diverse forms depression may take in persons with HFA/AS or the complexities of how one might make the diagnosis of depression in persons with comorbid HFA/AS. It should be pointed out, however, that because some features of depression and HFA/AS overlap, it is important to track that the changes in mood are a departure from baseline functioning. Thus, the presence of social withdrawal in a person with HFA/AS should not be considered a symptom of depression unless there is an acute decline from that person's baseline level of functioning. A second important point is that the core symptoms of depression should arise *together*. Thus, the simultaneous appearance of symptoms such as sleep and appetite changes, irritability, sadness, loss of pleasure in activities, decreased energy, further withdrawal from interactions, and self-deprecating statements would point to depression. An additional important point is that patients who display affective and vocal monotony are at higher risk for having their remarks minimized. Higher functioning individuals can make suicidal statements in a manner that suggests an off-hand remark, without emotional impact. When comments are made this way, clinicians and others may underestimate them. In persons with HFA/AS, the content of such comments may be more crucial than the emotional emphasis with which they are delivered.

Agents that are useful for treatment of depression in persons with HFA/AS are serotonin reuptake inhibitors (Table 1). There also may be indications for considering tricyclic agents with appropriate monitoring of ECG, pulse, and blood pressure (Table 5). There are no agents that have been shown to be particularly more beneficial for depressive symptoms in persons with HFA/AS. Thus, the decision as to which agents to use is determined by side effect profiles, previous experience, and, perhaps, responses to these medications in other family members.

Table 5
Tricyclic agents

Generic medication	Brand name	Dose range	Comments
Clomipramine	Anafranil	25–250 mg/d	Routine ECG monitoring essential. (Sudden death on desipramine) Tachycardia, postural hypotension, dry mouth, constipation, sedation. Blood level monitoring is helpful to achieve safe, proper dose.
Desipramine	Norpramine	10–250 mg/d	
Imipramine	Tofranil	10–300 mg/d	
Nortriptyline	Pamelor	5–150 mg/d	

Hyperactivity and inattention

Hyperactivity and inattention are common in HFA/AS individuals, particularly in early childhood [5,63,64]. Differential diagnostic considerations are paramount, particularly in the context of HFA/AS [63]. Hyperactivity and inattention is seen in a variety of other disorders, such as developmental receptive language disorders, anxiety, and depression. Thus, the appearance of inattention or hyperactivity does not point exclusively to attention deficit hyperactivity disorder (ADHD). The compatibility of the patient and his or her school curriculum is particularly important when evaluating symptoms of hyperactivity and inattention. There is a risk that a school program that is poorly matched to the individual's needs, by overestimating or underestimating a child's abilities, may be frustrating, boring, or unrewarding. If the verbal or social demands exceed what he or she can manage, they may produce anxiety or other problems that mimic inattention or induce hyperactivity.

Virtually every variety of medication has been tried to reduce hyperactive behavior and increase attention. The best evidence at this point supports dopamine blocking agents [39–46] (Table 4), stimulants [65] (Table 6), alpha-adrenergic agonists [35] (Table 2), and naltrexone [66–68] (Table 3).

Inflexibility and behavioral rigidity

Symptoms of inflexibility or behavioral rigidity are often difficult to quantify and yet often introduce some of the most disruptive chronic behaviors exhibited by patients with HFA/AS. These can be manifest by difficulties tolerating changes in routine, minor differences in the environment (such as changes in location for certain activities), or changes to plans that have been previously laid out. For some individuals this inflexibility can lead to aggression, or to extremes of frustration and anxiety that thwart activities. Families and school staff may find themselves "walking on eggshells" in an effort to circumvent any extreme reaction from brittle patients. In addition, the patients themselves may articulate their anxiety over fears that things will not go according to plan or that they will

Table 6
Stimulants

Generic medication	Brand name	Dose range	Comments
Methylphenidate	Ritalin, Concerta, and others	2.5–90 mg/d	Insomnia, anorexia, irritability, tics, agitation for all these forms of stimulants.
Dextroamphetamine	Dexedrine, Adderall and others	5–60 mg/d	
Pemoline	Cylert		"Black box" warning for liver toxicity. Risk profile has made most clinicians reluctant to consider pemoline.

be forced to make changes that they cannot handle. Sometimes these behaviors are identified as "obsessive-compulsive" because of the patient's need for ritualized order or nonfunctional routine. This is a phenomenologic error, as OCD has features that can be differentiated from PDD spectrum disorders [69]. Nevertheless, the idea that OCD and these "needs for sameness" might share some biologic features is attractive. It is not known now whether these symptoms are produced by disturbances in the same cortico-striatal-thalamo-cortical circuitry that is believed to produce OCD [70]. The model of obsessive-compulsive disorder, however, has suggested that use of SRI agents might be useful in ameliorating this problem [28,33]. Whether the effect of SRI agents on this symptom cluster is mediated by a general reduction in anxiety [48] or is specific for "needs for sameness" is not known. An alternative hypothesis suggests that the impairment might be located in circuitry subserving reward systems that rely on norepinephrine and dopamine [24,71]. If so, this would point to study of other agents and systems in future investigations.

To add further support to this hypothesis, reports from studies of alpha-adrenergic agents like clonidine [35] and guanfacine also suggest a decrease in these rigid behaviors. These short-term trials do not establish whether the benefits were sustained over a longer time, however. Agents that have been most useful are SRIs (Table 1), but there may be a role for dopamine blocking agents for refractory symptoms [43–45] (Table 4).

Stereotypies and perseveration

Stereotyped movements and repetitive behaviors are a common feature of HFA/AS [64]. As with behavioral rigidity and inflexibility, similar models for stereotypy and obsessive-compulsive disorder have been proposed [72]. Stereotypy also may be closely related to tic disorders and Parkinson disease, however, in which repetitive behaviors emerge from impairment in dopaminergic [73] and glutamaturgic systems [74]. There are also interesting analogs to L-dopa toxicity in Parkinson disease [75].

The treatments for stereotyped movements and perseveration closely parallel those for behavioral inflexibility and the two clusters are often grouped together in studies of treatment efficacy. Thus, serotonin reuptake inhibitors (Table 1) and alpha-adrenergic agonists may be helpful (Table 2). In addition, the hypothesis that dopamine might play a role suggests that dopaminergic blocking agents should be added to the possibilities (Table 4). Reports from studies of olanzapine [41], risperidone [42–44], and ziprasidone [45] suggest this is warranted.

Complementary and alternative medicine

The pharmacologic treatment of HFA/AS individuals is in a very early stage. As a result of more organized and systematic investigation, the field is making advances in the discovery of more effective treatments [76]. A large gap remains, however, between the need for effective treatments and the effectiveness of the

known agents. When there is such a disparity, opportunities for scientifically unfounded, anecdotal experience or highly biased efforts to capture the attention of parents, physicians, and educators are great. In the case of HFA/AS, one can cite many examples; the recent experience with secretin [77–80] is one. This does not mean that everything about secretin in autism is now understood, only that is unreasonable to recommend secretin for HFA/AS [81]. A similar point might be made for the variety of dietary and nutritional therapies—in the absence of carefully designed, scientifically valid, controlled studies, it is hard to justify recommending specific treatments.

Nevertheless, clinicians still have to answer families who ask about trying novel treatments. Among investigators and concerned practitioners, broad guidelines have been suggested (Klin, personal communication). The first is that treatments should be safe. A variety of diets and mineral supplements are apparently safe, but some can be toxic; the frequency of toxic reactions should be spelled out and signs of toxicity should be thoroughly comprehended. More extraordinary interventions such as neurosurgery obviously are not reversible. The second guideline is that treatments should be affordable. At the height of the secretin rush, some practitioners were charging many hundreds of dollars for medication and supplies that totaled less than fifty dollars. For most families, these treatments are not covered by insurance and money that goes to novel treatment is not available for other services. The third guideline is that novel treatments should not interfere with a child's participation in daily programs or treatments that are known to be helpful. Focusing on communication and social enhancement through education should be the first priority of every multimodal treatment plan. Attending school, having a detailed evaluation, and receiving behavioral supports that promote socialization and communication should not be curtailed by the pursuit of novel somatic, dietary, and complementary medical treatments.

Summary

The treatment of complex, polymorphous disorders like HFA/AS always brings a particular challenge to pharmacotherapy. Additionally, the specific characteristics presented by HFA/AS introduce unique complications to patient care and place unusual demands on a clinician's skill and experience. To provide safe and effective treatment, the clinician must understand the core features of the disorder and the manifestations of the condition in his or her patient. Furthermore, a thorough understanding of the family, school, and community resources and limitations is necessary.

Once an assessment has been made, focusing on target symptoms provides a crucial framework for care. Knowing manifestations of symptoms and characterizing their distribution and behavior in that patient is most important. For patients with HFA/AS it is particularly essential to coordinate behavioral and pharmacologic objectives. The target symptoms should be tracked carefully and placed into a priority system that is based on the risks and disability they create for the patient.

The skill of pharmacotherapy also means setting out realistic expectations, keeping track of the larger systems of care at school and home, and collaboration with parents and care providers.

There is an expanding range and pace of biologic and intervention research into HFA/AS. The genetic work has produced exciting leads that are likely to be helpful to future generations [82–84], but the task of clinicians is to tend to today's patients. As we discover more about the complex neural circuitry subserving repetitive behaviors, reward systems, and social cognition, there are good reasons to believe our treatments will become more sophisticated and specific. Psychopharmacology is also moving to design medications that target more specific populations of receptor and brain functions. This is likely to produce medicines that have fewer side effects, are more effective, and are more symptom-specific.

Pharmacotherapy is not the ultimate treatment for HFA/AS but it has a definite place. Medication can be a critical element in a comprehensive treatment plan. There is a wider range of medications with more specific biologic effects than ever before. For patients with HFA/AS these newer agents are safer and less disruptive. When paired with clinicians who are becoming more skilled at recognizing and managing symptoms, patients have a greater opportunity to reach their potential and lead pleasurable lives.

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