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Treatment of Aggression in Adults with Autism Spectrum Disorder: A Review

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Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by markedly impaired social interaction, impaired communication, and restricted/repetitive patterns of behavior, interests, and activities. In addition to challenges caused by core symptoms, maladaptive behaviors such as aggression can be associated with ASD and can further disrupt functioning and quality of life. For adults with ASD, these behaviors can portend adverse outcomes (e.g., harm to others or to the individual with ASD, hindering of employment opportunities, criminal justice system involvement). This article reviews the scientific literature to provide an update on evidence-based interventions for aggression in adults with ASD.

Method: A search of the electronic databases CINAHL, EMBASE, and PsycINFO was conducted using relevant search terms. After reviewing titles, abstracts, full-length articles, and reference lists, 70 articles were identified and reviewed.

Results: The strongest (controlled trial) evidence suggests beneficial effects of risperidone, propranolol, fluvoxamine, vigorous aerobic exercise, and dextromethorphan/quinidine for treating aggression in adults with ASD, with lower levels of evidence supporting behavioral interventions, multisensory environments, yokukansan, and other treatments.

Conclusions: Additional randomized, controlled trials using consistent methodology that adequately addresses sources of bias are needed to determine which treatments are reliably effective in addressing aggression in adults with ASD. In the meantime, considering efficacy and adverse effect/long-term risk profiles, a practical approach could start with functional assessment–informed behavioral interventions along with encouragement of regular, vigorous aerobic exercise to target aggression in adults with ASD, with pharmacotherapy employed if these interventions are unavailable or inadequate based on symptom acuity.

Keywords: adult, aggression, autism, treatment, violence

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by markedly impaired social interaction, impaired communication, and restricted/repetitive patterns of behavior, interests, and activities.[1] In addition to challenges caused by core symptoms of the disorder, maladaptive behaviors such as aggression can be associated with ASD and can further disrupt functioning and quality of life.[2,3] As most individuals with ASD will spend the majority of their lives with ASD as adults,[4,5] there is a compelling need for effective treatments for these maladaptive behaviors in adults in order to minimize adverse outcomes, which, in the case of aggression, can include harm to others or to the individual with ASD,[2,6,7] hindering of educational, employment, or housing opportunities,[2,3] and involvement with the criminal justice system.[6–8]

The *Diagnostic and Statistical Manual of Mental Disorders* (5th edition) (DSM-5) criteria for ASD require enduring deficits in social communication and interaction, along with restricted patterns of behavior, interests, or activities, starting in the early developmental period and causing significant functional impairment; intellectual and language impairment may or may not be present.[1] According to the Centers for Disease Control and Prevention, the prevalence of ASD among eight-year-old children in the United States in 2016 was 1.85%, representing a 27% increase from 2012 estimates (1.45%).[9] The recent increase in ASD prevalence further underscores the need to identify effective interventions to treat and prevent aggression in adults with ASD. Efforts in this regard have been under way for over two decades, using a variety of research approaches.

Current clinical approaches to the management of aggression in adults with ASD largely reflect the limited scientific literature in this area to date. A previous review by Kwok[10]

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focused on the use of medications to treat certain symptoms in individuals with ASD. Although accumulating evidence was noted for the use of second-generation antipsychotics and selective serotonin reuptake inhibitors to treat aggression (and repetitive and self-injurious behavior) in ASD, most (14 of 16) of the referenced studies pertained to *children* with ASD.

A review by Matson and colleagues[4] focused on applied behavior analysis (ABA) and pharmacotherapy to treat aggression and self-injury associated with ASD. The authors noted that because such behaviors usually have clear environmental antecedents, behavioral interventions, such as ABA, should be used to address them, with concurrent pharmacotherapy employed when environmental factors are unidentifiable or when challenging behaviors are very severe. They noted that only risperidone and aripiprazole were Food and Drug Administration (FDA)–approved for treating irritability associated with ASD in children (not adults). They did not reference non-ABA-based, non-pharmacologic interventions for treating aggression in ASD, and, like the Kwok review,[10] conclusions were based primarily on extrapolation from children's studies.

Another literature review by Matson and Jang[5] examining treatment of aggression in ASD found that, of 27 papers reviewed, only 5 explored this issue in adults with ASD, and no comment was made on the findings of these studies. The authors noted that the literature seemed to support using functional assessments and efforts to improve coping skills and competing behaviors in individuals with ASD and aggression, though this recommendation was based mostly on studies of children with ASD.

Eight systematic reviews have also been published regarding the treatment of aggression in individuals with ASD.[11–18] These reviews have suggested potential efficacy of atypical antipsychotics,[11,13,16,17] selective serotonin reuptake inhibitors,[12–14,17] beta blockers,[15] and psychoeducational interventions[18] for this purpose. However, the limited number of randomized, controlled trials, small sample sizes, and bias risks make it difficult to draw firm conclusions regarding the efficacy of specific treatments based on these reviews. Seven of these reviews focused solely on medication interventions,[11–17] and one focused exclusively on psychoeducational interventions.[18]

Thus, to date, previous literature reviews have focused primarily on controlled treatment studies of aggression in *children* with ASD, and prior systematic reviews have limited their scope to either studies of medication interventions *or* non-pharmacologic interventions, but not both, for treating aggression in adults with ASD. The present review aims to examine and summarize the scientific literature to provide a comprehensive update on all evidence-based interventions for aggression in adults with ASD. To our knowledge, this is the first attempt to summarize the evidence base on both non-pharmacologic and pharmacologic interventions for aggression in adults with ASD looking at a broad array of study designs. The review also considers implications of the findings for clinical practice. Of note, this review focuses specifically on treating *aggression* in adults with ASD, rather than treating general or core symptoms of ASD, the latter of which has been extensively studied and reported on in the current literature, and is beyond the scope of this review.

METHOD

A search of the databases CINAHL, EMBASE, and PsycINFO from January 1980 to February 2020 was conducted using the following search terms: autism, autistic, Asperger, pervasive developmental disorder, adult, aggression, violence, offending, treatment, and intervention. The resulting citations were included in the review if they met the following inclusion criteria: were treatment focused; included adult subjects; included subjects diagnosed with ASD (including by clinical or research diagnosis using DSM-III[19] criteria for infantile autism, DSM-III-R[20] criteria for Autistic Disorder, DSM-IV[21] or DSM-IV-TR[22] criteria for Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder Not Otherwise Specified, DSM-5[1] criteria for ASD, *International Statistical Classification of Diseases* (10th revision) [ICD-10][23] criteria for ASD, the Autism Diagnostic Interview–Revised [ADI-R],[24] the Autism Diagnostic Observation Schedule [ADOS],[25] the Autism Spectrum Quotient [AQ],[26] the Diagnostic Interview for Social and Communication Disorders,[27] the Asperger Syndrome Diagnostic Interview [ASDI],[28] or the Adult Asperger Assessment [AAA][29]); included subjects with aggression as a focus of treatment; were published in English; were articles (as opposed to posters or notes from conferences/symposiums); and were designed as case reports, N of 1 (nonrandomized) trials, prospective open trials, retrospective reviews, naturalistic case-control studies, or controlled trials. Citations not meeting all of these inclusion criteria were excluded from review.

The initial electronic search yielded a total of 429 reports. Three hundred fifty-nine of these were excluded after a review of titles and abstracts, leaving 70 records. Nineteen of these were subsequently excluded after reviewing full-length articles (3 for not being treatment focused, 3 for not involving adult subjects, 5 for not including subjects diagnosed with ASD, 5 for not having aggression as a focus of treatment, and 3 for not meeting study design criteria), leaving 51 citations. A review of reference lists and corresponding full-length articles yielded an additional 19 articles, resulting in a total of 70 articles included in this review.

DEFINITION AND ASSESSMENT OF AGGRESSION

In this review, *aggression* is defined as intentional threats, attempts, or infliction of bodily harm on another person, or intentional destruction of property. Self-injurious behavior is not included in the definition of *aggression* for the purposes of this article.

Of the 70 studies reviewed, 33 used standardized assessment instruments (e.g., rating scales or structured interview schedules) to measure aggression. The remaining studies assessed aggression via reports by caregivers, hospital staff, residential treatment staff, trained work counselors, day program staff, or study personnel on the observed frequency or intensity of aggressive behavior, with most of these studies

employing a specific definition of aggression for purposes of the study. These definitions all included an element of inflicting (or intending to inflict) physical harm on another person, with some variability as to the inclusion of self-injurious behavior or property destruction in the definition. The specific instruments and their reliability and validity in assessing aggression are briefly reviewed below.

Aberrant Behavior Checklist

The Aberrant Behavior Checklist (ABC)[30] is a 58-item checklist that measures six areas of behavior: irritability, lethargy, withdrawal, stereotyped behavior, hyperactivity, and inappropriate speech, and gives a total composite that has confirmed reliability and validity in regard to the factor structure, distribution of scores, and sensitivity to change. The Irritability subscale (ABC-I)[30] consists of 15 items on temper tantrums, aggression, mood swings, irritability, property destruction, and self-injury.

Behavior Problems Inventory

The Behavior Problems Inventory (BPI)[31] is a 51-item, informant-based, behavior-rating instrument for individuals with intellectual disabilities. It contains three subscales—Self-Injurious Behavior (14 items), Stereotyped Behavior (24 items), and Aggressive/Destructive Behavior (11 items), with items rated by frequency (0 = never, to 4 = hourly) and severity (0 = no problem, to 3 = severe problem). Various researchers have analyzed the psychometric properties of the BPI and have found acceptable to very good reliability and validity in measuring the above domains, including aggressive/destructive behavior.[32]

Behavioral Summarized Evaluation Scale for Autistic Disorder

The Behavioral Summarized Evaluation Scale for Autistic Disorder[33] is a 20-item, observer-rated instrument for assessing the presence of various behaviors (including aggression toward others) in individuals with ASD. Each item is scored on a scale from 0 to 4 (0 = behavior is never observed, 1 = behavior is sometimes observed, 2 = behavior is often observed, 3 = behavior is very often observed, 4 = behavior is always observed), with a total score obtained by summing the scores from the 20 individual items. Analyses of the scale's psychometric properties have revealed fair to excellent interrater reliability and acceptable content and criterion validity.[33]

Brown Aggression Scale

The Brown Aggression Scale (BAS)[34] is an informant-based instrument for assessing a history of aggressive behavior, with scores ranging from 0 = "non-occurrence" to 4 = "many, numerous, or multiple" aggressive events on each of nine categories, resulting in a total score range of 0 to 36. The specific categories include: (1) temper tantrums, (2) nonspecific fighting, (3) specific assaults (on people or property, but not suicidal attempts), (4) school discipline, (5) relationship with supervisors (civilian jobs), (6) antisocial behavior not involving police, (7) antisocial behavior involving police, (8) military disciplinary problems not involving military judicial system, and (9) difficulty with military judicial system. The scale has been demonstrated to have high interrater reliability and acceptable validity in measuring aggressive behavior.[34]

Clinical Global Impression Scale

The Clinical Global Impression (CGI)[35] scale is a well-established research rating tool that consists of two one-item measures evaluating (1) severity of psychopathology on a 1–7 scale (the CGI-Severity subscale [CGI-S][35]), with 1 = normal, not at all ill, 4 = moderately ill, and 7 = among the most extremely ill, and (2) change from the initiation of treatment on a similar 7-point scale (the CGI-Improvement subscale [CGI-I][35]), with 1 = very much improved since the initiation of treatment, 4 = no change from baseline (initiation of treatment), and 7 = very much worse since the initiation of treatment. The CGI[35] has been shown to correlate well with standard, well-known research drug-efficacy scales across a wide range of psychiatric indications, and has been shown to have reasonable reliability and validity in assessing and tracking changes in the severity of psychiatric symptoms (such as aggression) over time.[35]

Conners Abbreviated Parent-Teacher Questionnaire

The Conners Abbreviated Parent-Teacher Questionnaire (APTQ)[36] is a 10-item instrument that has been widely used to assess inattentive-hyperactive behaviors and the effects of medication on behavioral change. The items also elicit observations of behaviors associated with emotional lability, including temper outbursts and explosive behavior.[37] Each item features behavioral descriptions requiring a rating response in one of four categories: not at all (0), just a little (1), pretty much (2), and very much (3). Despite its wide usage, the psychometric properties of the Conners APTQ as a stand-alone behavioral rating instrument have received limited study, and concern has been raised regarding methodological issues, such as limitations associated with teacher reports (e.g., possible tendency to over- or underreport certain symptoms based on gender, although this concern mainly applied to inattentive/hyperactive symptoms and not to aggression).[37]

Harris Checklist for Challenging Behaviors

The Harris Checklist for Challenging Behaviors[38] is an instrument developed to measure the frequency, severity, and management difficulty associated with each of 12 aggressive behaviors in subjects with learning difficulties, with each item/behavior rated on a 5-point scale. This schedule was based on a review of the aggression literature, existing interview schedules and scales, and input from service providers working in a range of community and hospital facilities, and has demonstrated reasonable inter-informant, between-interviewer, and test-retest reliability.[38]

Maladaptive Behavior Scale

The Maladaptive Behavior Scale (MBS)[39] is an observer-rated instrument that rates the frequency of assaultive behavior toward others, self-injurious behavior, and property destruction,

and assesses the response of these behaviors to pharmacologic intervention at various time points. The scale is unpublished, and its psychometric properties, including reliability and validity for use in measuring aggression in a variety of contexts (e.g., outside of medication trials), are unclear.

Overt Aggression Scale

The Overt Aggression Scale (OAS)[40] is an instrument designed to measure categorical (as opposed to covert) aggression, including physical assaults on others, verbal threats of violence to others, self-injurious behavior, and explosive outbursts of property destruction. The OAS documents the frequency, intensity, and duration of an aggressive incident as well as any interventions taken with the subject because of aggressive behavior. This scale was developed using institutionalized child and adult psychiatric subjects. Reliability has been demonstrated by intra-class correlation coefficients ranging from .5 to .97 for verbal aggression and .72 to 1.00 for physical aggression.[40] The OAS has previously been used in the assessment of pediatric aggression and is medication sensitive.[41]

Positive and Negative Syndrome Scale

The Positive and Negative Syndrome Scale (PANSS)[42] is a 30-item rating scale that combines 18 items from the Brief Psychiatric Rating Scale (BPRS)[43] and 12 items from the Psychopathology Rating Schedule (PRS).[44] It is designed to provide an interview-based, accurate assessment of psychopathology, including positive schizophrenia spectrum symptoms (such as hallucinations and delusions) and negative symptoms (such as flat affect and psychomotor retardation). Factor analyses have converged on five major factors assessed by the PANSS: positive symptoms, negative symptoms, disorganization, affect, and resistance or activation (including hostility, poor impulse control, excitement, and uncooperativeness). Psychometric testing of the PANSS has demonstrated good test-retest reliability, moderate to good interrater reliability, and reasonable validity for the above subscales.[45] Its use in diagnostic contexts other than schizophrenia spectrum disorders, however, has been limited.[42]

Self-Injurious Behavior Questionnaire

The Self-Injurious Behavior Questionnaire (SIB-Q)[46] is a 25-item, clinician-rated instrument that assesses self-injurious behavior, physical aggression toward others, destruction of property, and other maladaptive behaviors. Each item is assigned a score ranging from 0 (not a problem) to 4 (severe problem), resulting in a total score ranging from 0 to 100. Despite its use in three of the studies reviewed,[46–48] the SIB-Q is an unpublished instrument, and as such, its psychometric properties, including reliability and validity, are unclear.

Vineland Adaptive Behavior Scale–Maladaptive Behavior Subscale

The Vineland Adaptive Behavior Scale–Maladaptive Behavior Subscale[49] consists of two parts, one pertaining to symptoms of aggression, withdrawal, tantrums, inattention, emotionality, and defiance, and the other related to self-injury, property destruction, mannerisms, preoccupations, and rocking. The instrument is completed by a qualified professional and has been shown to have reasonable reliability and validity in assessing maladaptive behavior (including aggressiveness) in individuals with ASD.[50]

Visual Analog Scale

The Visual Analog Scale (VAS)[51] is a 12-item clinician-rated instrument assessing individuals on a number of measures, including the following: aggressive, anxious/nervous, calm, restless, irritable, depressed, fearful, social interaction, eye contact, talkative, tired, and happy. It has been employed in studies of response to pharmacologic intervention in individuals with ASD.[47,52] Its psychometric properties, including reliability and validity, are unclear, at least based on the available published literature.

ASSESSMENT OF COMORBID PSYCHIATRIC DIAGNOSES

A small proportion (5 of 70) of the studies reviewed here used standardized assessment instruments to assess for comorbid psychiatric diagnoses, which have been shown to be a frequent factor associated with aggressive behavior in individuals with ASD.[53] Specifically, 2 of 21 case reports,[54,55] 2 of 17 N of 1 nonrandomized trials,[56,57] 1 of 16 prospective open trials,[58] none of 8 retrospective reviews, and none of 7 randomized, controlled trials employed such instruments to determine diagnostic comorbidity. The specific instruments used included the Millon Multiaxial Personality Inventory (MCMI-III),[59] Positive and Negative Syndrome Scale (PANSS),[42] Mini Psychological Assessment Scale for Adults with Developmental Disabilities (Mini PAS–ADD),[60] Health of the Nation Outcome Survey–Learning Disabilities (HoNOS-LD),[61] and Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[62] The PANSS[42,45] has been described earlier in this review (see "Definition and Assessment of Aggression" section); the other instruments are briefly reviewed below.

The Millon Multiaxial Personality Inventory, Third Edition,[59] is a 175-item true/false self-report measure of 14 personality patterns and 10 clinical syndromes for use with adults aged 18 years and over being evaluated in mental health settings. It is designed to match the DSM-IV diagnostic criteria for each personality disorder and clinical syndrome cited. However, the reliability and validity of the MCMI-III in individuals with ASD, as with all self-report personality measures for individuals with ASD, remains unknown.

The Mini Psychological Assessment Scale for Adults with Developmental Disabilities[60] is an assessment schedule for psychiatric disorders in individuals with intellectual disability. It comprises 86 psychiatric symptoms generating a series of subscores on the following diagnostic areas: depression, anxiety, mania, obsessive-compulsive disorder, psychosis, unspecified disorder (including dementia), and pervasive developmental disorder (autism). It has been shown to have good validity and

interrater reliability in identifying possible co-occurring depression, anxiety, and mania in intellectually disabled individuals.[60]

The Health of the Nation Outcome Survey–Learning Disabilities[61] is a widely used, 18-item measure of mental health status in people with intellectual disability. The scale measures a wide range of behavioral and psychiatric symptoms, as well as independent functioning and relationships-based indicators of mental health functioning. Each of the 18 scales is scored from 0 to 4, with 0 indicating no problem; 1, minor problem requiring no action; 2, mild problem but definitely present; 3, moderately severe problem; and 4, severe to very severe problem. The scale has been shown to have high interrater reliability and strong internal consistency.[61]

The Structured Clinical Interview for DSM-IV Axis I Disorders[62] is a semistructured interview guide for making diagnoses of Axis I psychiatric disorders according to DSM-IV[21] diagnostic criteria. It is designed to be administered by a mental health professional, although trained research assistants may also administer the tool. It has been shown to have good reliability and fair validity, at least in research settings.[62]

Those studies not utilizing a standardized assessment instrument to assess for comorbid psychiatric diagnoses either used clinical interviews, record reviews, or other sources of collateral information (with or without DSM-III,[19] DSM-III-R,[20] or DSM-IV[21] criteria applied to this information) to ascertain the presence of such comorbidity (19 studies), or did not clearly assess for such comorbidity (46 studies). In this review, the presence of comorbid psychiatric diagnoses did not appear to have a substantial impact on the outcomes (i.e., responses to interventions to treat aggression) of the reviewed studies. However, as above, the number of studies assessing comorbidity (24 of 70) was relatively small, and there are challenges in the accurate assessment of comorbidity in individuals with ASD; for example, some "comorbid" diagnoses, such as obsessive-compulsive disorder or intermittent explosive disorder, may have been based on behaviors rooted in the ASD diagnosis itself, rather than separate co-occurring psychiatric disorders.[63]

While this review was not intended to be a systematic review or meta-analysis, for the purpose of facilitating a useful summary and interpretation of the findings, an attempt was made to evaluate the quality and risk of bias of the included studies by incorporating standards highlighted in the Cochrane Collaboration's tool for assessing risk of bias in randomized trials,[64] Cochrane ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool for assessing risk of bias in nonrandomized treatment studies,[65] and Reichow tool for assessing risk of bias in single-case research design.[66] The results of these assessments are presented in Supplemental Tables 1, http://links.lww.com/HRP/A137, 2, http://links.lww.com/HRP/A138, and 3, http://links.lww.com/HRP/A139, and discussed in the Results section below.

RESULTS

To date, there have been 21 case reports,[52,54,55,67–84] 17 N of 1 nonrandomized trials,[56,57,85–99] 16 prospective open trials,[41,46,47,58,100–111] 8 retrospective reviews,[39,112–118] 1 naturalistic case-control study,[119] and 7 randomized, controlled trials[48,120–125] of treatments for aggression in adults with ASD.

Case Reports

Table 1 summarizes the 21 case reports[52,54,55,67–84] that were reviewed regarding treatments for aggression in adults with ASD. These reports describe various interventions of potential benefit, including behavioral interventions such as differential reinforcement of other behavior (DRO) schedules,[67] community interventions such as integrated assessment and treatment services,[81] pharmacologic interventions such as risperidone,[72–74] aripiprazole,[76,77,82] clozapine,[52,55] buspirone,[71,78] propranolol,[68] clonidine,[70] riluzole,[80] and methadone,[75] and electroconvulsive therapy (ECT).[84] Of note, 2 of the 3 cited case reports examining the use of risperidone in treating aggression in adults with ASD described 3 subjects each,[72,73] so that these 3 case reports actually comprised a total of 7 subjects (3 from each of 2 case series and 1 single-subject case report). Similarly, the one case report describing the use of propranolol[68] contained descriptions of 5 subjects; the case report on clomipramine described 2 subjects;[69] the report on riluzole described 2 subjects;[80] the Jordan and colleagues report[82] on aripiprazole described 2 subjects; and the report on ECT described 2 subjects.[84]

As shown in Supplemental Table 1, http://links.lww.com/HRP/A137, all of the studies were judged to be at low risk of bias regarding participant selection (i.e., individuals selected for the study were appropriate and in need of the intervention), selective outcome reporting (i.e., outcome data were presented for all participants who started the study, not just those who completed it), and data sampling (i.e., there were an adequate number of data points to establish the level, trend, and variability of the data), and all but four studies[54,73,74,83] were at low risk of bias regarding procedural fidelity (i.e., experimental conditions were described with replicable precision, and study procedures were adhered to). Most of the studies, however, did not randomly allocate subjects to intervention conditions (or to the order of conditions to which subjects were exposed), blind participants and personnel, blind outcome assessment, or ensure dependent-variable reliability (i.e., measures to estimate interrater agreement regarding the dependent variable of aggression). Moreover, the uncontrolled nature of these reports makes it difficult to draw firm conclusions about the efficacy of the interventions described, and the small sample sizes limit the generalizability of the findings. Nonetheless, such reports suggest interventions that may merit controlled study.

N of 1 Nonrandomized Trials

Table 2 summarizes the 17 N of 1 trials[56,57,85–99] that were reviewed regarding treatments for aggression in adults with ASD. These trials—primarily nonrandomized and crossover in nature—suggest potential usefulness of propranolol,[89] behavioral interventions (such as DRO schedules,[88,91,92,94

Table 1

Case Reports of Treatments for Aggression in Adults with Autism Spectrum Disorder

Study	Diagnosis	Nature of aggression	Intervention	Outcome
Smith (1985)[67]	Subject 1: Autism (DSM-III[19]) Severe ID (IQ = 51) 22 y.o. man	Hitting and kicking others	Scheduled positive reinforcement of desirable behavior (e.g., providing favorite foods, drinks, activities, or staff attention every 15 minutes) Picture schedules Verbal/physical redirection for aggressive behavior (e.g., to return to task at hand)	Substantial reduction in frequency of aggressive incidents (from mean of 19/day during first month to mean of less than 1/day during sixth month)
	Subject 2: Autism (DSM-III[19]) Minimally verbal (2- to 3-word phrases) 18 y.o. man	Aggression (unspecified), severe self-injury	Combination of differential reinforcement of other behavior (in which subject was provided positive reinforcement every 3 minutes if not hitting others or himself) Free access to food upon request (to reinforce asking rather than hitting for food) Reinforcement for working on task (rather than being asked to complete tasks, which served as antecedent to aggression)	Substantial reduction in frequency of aggressive behaviors as measured by increase in proportion of time spent using hands in nonaggressive activities (over 90% by day 16)
Ratey et al. (1987)[68]	Subject 1: Autism (DSM-III[19]) 31 y.o. man	Assaulting others, window breaking, head banging	Propranolol 360 mg/day for 11 months	Substantial reduction in frequency of aggressive episodes
	Subject 2: Autism (DSM-III[19]) 30 y.o. man	Uncontrollable aggressive behavior toward halfway house and hospital staff (not specified)	Propranolol 360 mg/day for 1 month	Elimination of aggressive behavior toward hospital staff
	Subject 3: Autism (DSM-III[19]) 24 y.o. man	Assaulting residential program staff, punching holes in walls	Propranolol 100 mg/day for 1 year	Substantial reduction in frequency of aggressive behavior (from 48 to 29 incidents/month, with 50% reduction in use of restraint wraps)
	Subject 4: Autism (DSM-III[19]) 25 y.o. woman	Biting and scratching others, head banging	Propranolol 180 mg/day for 18 months	Substantial reduction in frequency of aggressive behavior (from 7 to 2.5 incidents/month)
	Subject 5: Autism (DSM-III[19]) 35 y.o. man	Assaultive behavior toward family and staff, property destruction	Propranolol 160 mg/day (duration unspecified)	Resolution of aggressive behavior; eventually switched to nadolol for dosing convenience, with no change in clinical gains over 2 months
McDougle et al. (1992)[69]	Subject 1: Autistic disorder (DSM-III-R[20]) Severe ID 27 y.o. man	Aggressive behavior toward others when rituals were interrupted (ritualistic furniture arranging and dish cleaning)	Clomipramine up to 250 mg/day for 12 weeks	Substantial improvement in aggression, ritualistic behavior, and social interaction skills, with improvements maintained

Table 1

Continued

Study	Diagnosis	Nature of aggression	Intervention	Outcome
				over 17-month follow-up period
	Subject 2: Autistic disorder (DSM-III-R[20]) 24 y.o. man	Aggressive behavior toward others when rituals were interrupted (ritualistic scanning of television channels and recording of television program dates, times, and stations)	Clomipramine up to 250 mg/day for 4 months	No notable improvement in aggression, social relatedness, ritualistic behavior during 4 months of treatment
Koshes & Rock (1994)[70]	Autistic disorder (DSM-III-R[20]) Intermittent explosive disorder 26 y.o. woman	Aggressive behavior toward caretakers, other patients in institutional settings, and children (e.g., dragging child by the hair)	Clonidine 0.4–0.6 mg/day orally for 4 weeks, followed by 0.6 mg/day via transdermal patch for several weeks	Substantial reduction in aggressive outbursts; improved alertness and verbal output
Hillbrand & Scott (1995)[71]	Autism (DSM-III[19]) Mild ID 41 y.o. man	Head-butting others, property destruction (destroyed sinks with feet)	Buspirone up to 80 mg/day for 4 months (added to haloperidol, phenytoin, and imipramine)	Marked reduction in aggressive behavior, with corresponding dramatic reduction in use of seclusion or restraints Clinical gains maintained at 2-year follow-up
McDougle et al. (1995)[72]	Subject 1: Autistic disorder (DSM-IV;[21] corroborated with ADI-R[24] and ADOS[25]) Mild ID 20 y.o. man	Assaulted mother with fire poker at home; in hospital, punched two peers, threw billiard ball at another peer, kicked trash can across room	Risperidone up to 6 mg/day for 7 days	Substantial improvement in aggression, social interaction skills, and repetitive behavior, maintained 12 months after discharge from hospital
	Subject 2: PDD NOS (DSM-IV;[21] corroborated with ADI-R[24] and ADOS[25]) 44 y.o. woman	Hit father, pushed mother down stairs	Risperidone up to 8 mg/day for 10 days	Substantial improvement in aggression, social interaction skills, and all-encompassing fixation on astrology and historical battles, maintained 15 months after discharge from hospital
	Subject 3: Autistic disorder (DSM-IV;[21] corroborated with ADI-R[24] and ADOS[25]) 31 y.o. man	Aggression toward peers and staff at group home (necessitating restraints 8–10 times/day) and toward self (striking ears with fists, banging head against walls and floor)	Risperidone 2 mg/day for 7 days	Marked reduction in aggression, repetitive behavior, and ability to vocalize needs, sustained 12 months later
McCartney et al. (1999)[73]	Subject 1: Autistic disorder (DSM-IV[21]) Severe ID 27 y.o. man	Aggression (slapping, nipping parents and other caregivers, throwing objects)	Risperidone up to 5 mg/day for 15 months	Substantial reduction in frequency of aggressive outbursts
	Subject 2: Autistic disorder (DSM-IV[21])	Aggression (unspecified; "dangerous, impulsive actions" requiring restraint in wheelchair)	Risperidone up to 8 mg/day for 16 months	Substantial reduction in aggression (e.g., able to go out with family)

Table 1

Continued

Study	Diagnosis	Nature of aggression	Intervention	Outcome
	19 y.o. man			
	Subject 3: Autistic disorder (DSM-IV[21]) 40 y.o. woman	Aggression (scratching, biting others, property damage)	Risperidone 0.5 mg twice daily for 1 month	Substantial reduction in aggression (able to go out to seaside and to lunch, have visits with father)
Gobbi & Pulvirenti (2001)[52]	Autistic disorder (DSM-IV[21]) Profound ID (IQ = 20) 32 y.o. man	Aggression (hurting parents, destroying property)	Clozapine 200 mg/day (titrated over 6 weeks) for 5 years	Marked reduction in aggression as measured by change in Visual Analog Scale[51] aggression score from 95 to 15 after 5 years of treatment
Raheja et al. (2002)[74]	Asperger's syndrome (ICD-10[23]) 30 y.o. man	Aggression (attempted bombing of residence, making death threats)	Risperidone 1 mg/ml per day (1 mg/day) for 6 months	Substantial reduction in frequency of aggressive behavior (from 2–3 episodes/week to 1 per 2 months), social relations, and repetitive thinking
Hasan et al. (2006)[75]	Autistic disorder (DSM-IV[21]) Profound ID 35 y.o. woman	Attacking others to point of requiring physical restraints for much of two-year hospitalization; repeatedly hitting head against wall; required four staff members to feed, clothe, and bathe her	Methadone 20 mg orally 3 times daily for 8 weeks	Dramatic reduction in aggression, need for restraint, and self-injurious behavior (effects observed within days) Able to eat and dress Discharged to group home 8 weeks later, where continued to function above baseline with superior quality of life
Shastri et al. (2006)[76]	ASD (criteria unspecified) Severe ID 38 y.o. man	Frequent, aggressive attacks on staff members in 24-hour supported accommodation whenever routine changed	Aripiprazole 15 mg/day for approximately 3 months (aggression failed to adequately respond to risperidone 6 mg daily + chlorpromazine 100 mg 3 times daily; on this regimen gained 65.3 kg and had excessive fatigue)	After initial increase in aggression toward staff during first 6 weeks, substantial improvement in frequency and severity of aggressive behavior (from 4–5 incidents/week to 1–2 incidents/month), sustained several months later Less fatigued and had lost 12.7 kg
Dratcu et al. (2007)[77]	Asperger's syndrome (DSM-IV;[21] corroborated by Autism Spectrum Quotient[26])	Threatening staff at hostel with knife	Aripiprazole titrated to 15 mg/day for 3 weeks	Substantial improvement in anger, irritability, suspiciousness, and ability to comfortably interact with others by fourth week of treatment Improvements sustained for several months following discharge back to hostel
Brahm et al. (2008)[78]	Autistic disorder (DSM-IV[21]) Profound ID (IQ < 20–25) 33 y.o. woman	Aggression (head-butting others, destroying property)	Buspirone up to 90 mg/day for several months	Substantial reduction in frequency of aggressive behavior (from 250 to 25 incidents/month)

Table 1

Continued

Study	Diagnosis	Nature of aggression	Intervention	Outcome
Stigler et al. (2010)[79]	Autistic disorder (DSM-IV-TR[22]) Moderate ID 20 y.o. man	Aggression, self-injurious behavior (head banging), tantrums	Paliperidone 12 mg/day for 42 weeks (no titration employed)	Marked improvement in aggression, self-injurious behavior, tantrums in multiple settings, reflected by CGI-I[35] of 2
Murphy (2010)[54]	ASD (Diagnostic Instrument for Social and Communication Disorders,[27] ASDI,[28] Adult Asperger's Assessment[29])	Aggression (stabbed work supervisor to death, punched a teenaged girl)	Education about ASD Adapted cognitive-behavioral therapy Skills development involving emotion recognition, general problem solving, recognizing and appreciating consequences of actions on others, victim empathy, dealing with interpersonal conflict, and anger expression	Continued to express extremely egocentric perspective, with no victim empathy (i.e., prominent social-cognitive deficits)
Wink et al. (2011)[80]	Subject 1: Autistic disorder (DSM-IV[21]) Moderate ID 18 y.o. man	Aggression (not specified), self-injurious behavior (not specified), irritability, severe repetitive behaviors	Aripiprazole 20 mg/day (prescribed previously for aggression and self-injurious behavior); riluzole 100 mg/day for 24 weeks was added	Substantial improvement in aggression and self-injurious behavior on aripiprazole 50% reduction in repetitive movements and touching with addition of riluzole (reflected by CGI-I[35] of 2/"much improved" at 4 weeks and thereafter)
	Subject 2: Autistic disorder (DSM-IV[21]) Severe ID 20 y.o. man	Hitting, kicking, biting others; repetitive head banging and slapping self (necessitating use of helmet and padded room); repetitive play with fecal matter	Riluzole 100 mg twice daily for 8 weeks (added to existing regimen of paliperidone 9 mg/day, olanzapine 40 mg/day, clonidine 0.6 mg/day, carbamazepine 800 mg/day, amitriptyline 75 mg/day, naltrexone 50 mg/day)	Substantial reduction in aggressive and self-injurious behavior after 1 month 50% reduction in repetitive behaviors at 2 months (reflected by CGI-I[35] of 1/"very much improved" at 2 months and thereafter)
Yanartas et al. (2011)[55]	Asperger's syndrome (DSM-IV[21]) Schizophrenia 26 y.o. man	Aggression (hitting and beating relatives), psychotic symptoms	Clozapine up to 200 mg/day for 7 weeks	Substantial improvement in aggression and psychotic symptoms as reflected by change in PANSS[42] score from 109 to 65
Richings et al. (2011)[81]	Autistic disorder (DSM-IV[21]) ID (53% mild, 35% moderate, 11% severe) 35 adults	Aggressive behavior (not specified)	Integrated assessment and treatment service consisting of combination of outreach, day assessment, and inpatient services, with close coordination between local community learning-disability specialist teams, day assessment providers, inpatient providers, and existing placement staff	Substantial reduction in frequency of aggressive incidents on inpatient unit (from 15 to 5/month), and decrease in length of hospital stays and number of admissions, both during 2 years of initial implementation
Jordan et al. (2012)[82]	Subject 1:	Aggression (unspecified), compulsive exercise,	Aripiprazole 10 mg/day (initially added to existing	Substantial additional reduction (beyond effects of

Table 1

Continued

Study	Diagnosis	Nature of aggression	Intervention	Outcome
	ASD (ICD-10;[23] corroborated with ADI-R[24] and ADOS[25]) 27 y.o. man	paranoia, ideas of reference	regimen of clozapine, which was discontinued due to neutropenia) and subsequently increased to 30 mg/day for 1 month	clozapine) in aggression and paranoia Marked improvement in compulsive behaviors on 30 mg/day, sustained at 4 months Improvement equivalent to CGI-I[35] of 1 ("very much improved")
	Subject 2: Asperger's syndrome (ICD-10;[23] corroborated with ADI-R[24] and ADOS[25]) 20 y.o. woman	Sudden outbursts of verbal and physical aggression, irritability, agitation	Aripiprazole 10 mg/day for 2 weeks	Substantial reduction in the frequency of aggressive outbursts (from 2–3/week to <1/month) Improvement equivalent to CGI-I[35] of 1 ("very much improved")
Petrosino et al. (2016)[83]	ASD (DSM-5[1]) Severe ID 32 y.o. man	Physical aggression, psychomotor agitation, self-injurious behavior	Pipamperone (dose unspecified)	Drastic reduction in aggression and self-injurious behavior as measured by changes in CGI-S,[35] CGI-I,[35] and ABC[30] without extrapyramidal side effects Also associated with improved social functioning Gains maintained at 6-month follow-up
Sajith et al. (2017)[84]	Subject 1: ASD (DSM-5[1]) Mild ID 21 y.o. man	Aggression (scratching others), self-injurious behavior	ECT (unilateral) × 11 treatments, followed by another course of 8 treatments (while continuing risperidone 4 mg/day and chlorpromazine 150 mg/day)	Substantial reduction in frequency and intensity of aggressive and self-injurious behaviors as measured by marked improvements in ABC[30] scores pre- to post-ECT However, aggression recurred after discontinuation of ECT
	Subject 2: ASD (DSM-5[1]) Moderate ID 23 y.o. man	Aggression (scratching and pulling hair), self-injurious behavior	ECT (unilateral) × 12 treatments, followed by another course of 12 treatments (while continuing risperidone 6 mg/day)	Substantial reduction in frequency and intensity of aggression and self-injurious behavior after second course, as measured by ABC[30] scores pre- and post-ECT Improvements maintained with weekly ECT treatments for 2 months

ABC, Aberrant Behavior Checklist; ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; ASDI, Autism Spectrum Diagnostic Interview; AQ, Autism Spectrum Quotient; CGI-I/S, Clinical Global Impression Scale–Improvement/Severity; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ECT, electroconvulsive therapy; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, 10th revision; ID, intellectual disability; IQ, intelligence quotient; PANSS, Positive and Negative Symptom Scale; PDD NOS, pervasive developmental disorder not otherwise specified; y.o., year old.

positive behavioral support programs,[56,57] nonexclusionary time-out procedures,[86] behavioral report cards,[87] use of "do" versus "don't" requests to interrupt aggressive behavior,[95] provision of social comments prior to task demands,[93] task analysis/forward-chaining with prompt stimulus fading,[99] and electromyographic [EMG] response discrimination biofeedback training[85]), multisensory environments,[96] and physical exercise.[90]

As shown in Supplemental Table 2, http://links.lww.com/HRP/A138, most of these studies were assessed to be at low risk of bias involving selection of study participants, misclassification of interventions, deviation from intended interventions, and missing outcome data, and to be at moderate risk of bias involving selective reporting. All but two of the studies,[89,96] however, were judged to be at moderate to serious risk of bias involving measurement of outcome data (i.e., the outcome measure was vulnerable to influence by knowledge of the intervention received, and the outcome assessors were aware of the intervention received by participants).

In the Cohen and colleagues[89] study demonstrating reduced frequency of aggressive behavior with long-acting propranolol compared to placebo in an adult with ASD and fragile X syndrome, the subject and assessors were blind to which intervention the subject received, according a low risk of bias regarding measurement of outcome data to this study. However, the study examined a single subject with fragile X syndrome, possibly limiting its generalizability to adults with ASD without this genetic condition.

In the Kaplan and colleagues[96] study showing a slight reduction in aggressive behavior following exposure to a multisensory (Snoezelen) environment in 2 of 3 adults with ASD and intellectual disability, the use of blinded outcome assessors conferred a low risk of bias involving measurement of outcome data to this study. Its small sample size, however, may limit the generalizability of the results.

Finally, 10 of the 17 studies[56,57,85–88,90,91,93,98] were judged to be at serious risk of bias due to baseline or time-varying confounding (i.e., at least one known important confounding domain was not measured or controlled for), while the remaining 7 studies[89,92,94–97,99] were assessed to be at moderate risk of bias in this regard (i.e., confounding was expected, but all known important confounding domains were appropriately measured and controlled for). Overall, the nonrandomized nature of most of these studies makes it difficult to firmly conclude that the interventions studied were responsible for the effects observed and to exclude other factors that could have accounted for the outcomes. Within the constraints imposed by these bias and design limitations, evidence from nonrandomized, N of 1 studies provides preliminary support for propranolol and multisensory environments, and to a somewhat lesser extent, behavioral interventions, in addressing aggressive behavior in adults with ASD.

Prospective Open Trials

Table 3 summarizes the 16 prospective, open trials[41,46,47,58,100–111] that were reviewed regarding treatments for aggression in adults with ASD. Demographic information for the samples in each study (including sex distribution and mean age) is included in the table. These trials suggest potential usefulness of multisensory environments,[109] beta blockers,[41,100,101] clomipramine,[104] sertraline,[46,103] risperidone,[105–107] olanzapine,[47] paliperidone,[111] and the Japanese herbal preparation yokukansan.[58,110]

As seen in Supplemental Table 2, http://links.lww.com/HRP/A138, all of these trials were judged to be at low risk of bias with regard to selection of study participants, misclassification of interventions, deviation from intended interventions, and missing outcome data, and to be at moderate risk of bias involving selective reporting. All but two of the studies,[58,109] however, were judged to be at moderate to serious risk of bias involving measurement of outcome data, and all but two of the studies[46,104] were assessed to be at serious risk of bias due to baseline or time-varying confounding.

The Fava and Strauss[109] study examined two different multisensory environments (a Snoezelen room and a stimulus preference room) in treating disruptive (including aggressive) behavior in 27 adults with profound intellectual disability (9 of whom were diagnosed with autism). The Snoezelen room is a type of multisensory environment designed to stimulate the senses through light, sound, touch, and smell, creating a feeling of safety and providing novel sensations that are under the user's control. The room in this study contained a rocking chair, vibrating pillow, kaleidoscope-like color wheel, lava lamp, beanbags, tactile books with textures, rain sticks, aromatherapy oils, and other items designed for this purpose, with subjects interacting with these stimuli in a free, unstructured manner, supported by a caregiver present in the room. The stimulus preference room is another type of multisensory environment that differs from a Snoezelen room in that stimuli have already been selected by the user during using a preference assessment conducted prior to use of the room, and caregivers interact with the user in a more structured manner, using verbal and physical prompts regarding the behaviors learned by users toward their preferred stimuli and themselves. The study showed that use of the Snoezelen room was associated with a decrease in aggressive behaviors in individuals with ASD, whereas the stimulus preference room was associated with reduced aggressive behavior only in individuals with profound intellectual disability without ASD. Aggressive behaviors were scored using videotaped recordings of experimental sessions by three blind observers who were unaware of the purpose of the experiment and who were not familiar with the participants. While the study thus employed blinded outcome assessment and was therefore judged to be at low risk of bias involving measurement of outcomes, it was deemed at serious risk of bias due to baseline or time-varying confounding, in that the effect of specific types of caregiver attention provided in the Snoezelen intervention was not adequately measured or controlled for.

In the Miyaoka and colleagues[58] study showing beneficial effects of yokukansan (TJ-54), a Japanese herbal medicine, in treating aggression in 36 of 40 children, adolescents, and

Table 2

N of 1 (Nonrandomized) Trials of Treatments for Aggression in Adults with Autism Spectrum Disorder

Study	Diagnosis	Nature of aggression	Study design	Intervention	Outcome	Limitations
Hughes & Davis (1980)[85]	Autistic disorder (DSM-III[19])	Hitting and kicking others, batting with head, throwing objects	A-B-A	Training subject to attempt to relax in face of aggression-inducing stimuli by providing verbal praise and positive reinforcement (pennies) each time subject attempted to relax Awareness of relaxation status/attempts conveyed to subject via electromyographic biofeedback	Marked reduction in number and frequency of aggressive responses (from 19 during first 4 baseline sessions to 6.25 during first 4 intervention sessions, to 13 during next set of baseline sessions, which, although higher than during preceding sessions, represented improvement from initial baseline)	Lack of control procedures used to assess contribution of habituation alone (i.e., continued presence of an aggression-provoking stimulus) in producing observed reduction in aggressive responses (i.e., time-varying confounding) Unblinded outcome assessors
McKeegan et al. (1984)[86]	Autism (DSM-III[19]) Profound ID 24 y.o. man	Aggressive and self-injurious behavior (unspecified)	A-B (quasi-experimental with extended follow-up)	Non-exclusionary timeout program: 2-minute period during which ribbon (and associated edible- and praise-based reinforcement of appropriate behavior) removed from subject upon occurrence of aggressive behavior	Substantial decrease in aggressive behavior, with clinical gains maintained at 25-day (mean = 0.25 occurrences/hour) and 6-month (mean = 0 occurrences/hour) follow-up assessments	Quasi-experimental design makes it difficult to exclude other explanations (i.e., unidentified variables) for reduction in aggression (i.e., time-varying confounding) Unblinded outcome assessors
Smith & Coleman (1986)[87]	Autism (DSM-III[19]) Moderate ID (IQ = 52) 26 y.o. man	Aggressive behavior (hitting others, destroying property) in job setting	A-B (quasi-experimental with extended follow-up)	Subject received report card: Rated each hour on relevant job-appropriate behaviors (e.g., no hitting or kicking people, no property destruction), with subject earning 1 or 0 for each report card item each hour If all points earned during week, "successful week meeting" held with his favorite staff members	Substantial reduction in aggressive behavior: During baseline period (weeks 1 to 7), subject earned average of 28 points; during first week of treatment, increased to 48 points; by week 22, began to regularly earn maximum number of 52 points	Presence of full-time, trained counselor in work environment may be required to maintain treatment gains Cannot exclude time-varying confounding Outcome assessors not identified
McNally et al. (1988)[88]	Autism (criteria unspecified) Severe ID 24 y.o. woman	Aggressive behavior (kicking others), polydipsia	A-B	DRO schedule: At 30-minute assessment intervals, subject received tangible reinforcers (e.g., gum, candy, mustard,	Substantial reduction in frequency of aggressive behaviors beginning at 4 weeks and maintained at 29-week follow-up, coinciding with reduction	Due to A-B design, difficult to determine whether improvement in aggression due to intervention versus other effects associated

Table 2

Continued

Study	Diagnosis	Nature of aggression	Study design	Intervention	Outcome	Limitations
				absence of work activity) for choosing to refuse water	in polydipsic behavior (which was thought to be driving aggression due to frustration at redirection)	with passage of time (i.e. time-varying confounding) Outcome assessors not identified
Cohen et al. (1991)[89]	Pervasive developmental disorder (DSM-III-R[20]) Severe ID (Stanford-Binet IQ = 28) Fragile X syndrome 32 y.o. man	Aggression toward others, property destruction, self-injurious behavior	A-B-A	Propranolol LA at dose of 80–320 mg daily over 11 weeks, preceded and followed by 2-week and 11-week placebo periods, respectively	Reduction in frequency of aggressive incidents, declining from baseline average rate of 1.7 events per week, and increasing posttreatment to average of 1.33 incidents per week when subject was returned to placebo	Because study focused on subject with fragile X syndrome, may have limited generalizability to adults with ASD without this genetic condition Did not control for possible synergistic effect of haloperidol + propranolol
Allison et al. (1991)[90]	Autistic disorder (DSM-III-R[20]) Severe ID 24 y.o. man	Grabbing, hitting, kicking, scratching, biting others in an intermediate care facility	Modified A-B-A-B	Physical exercise (consisting of jogging resulting in heart rate elevations to 60%–80% of maximum) for 20 minutes daily over 14 days compared to 14-day periods of no intervention	Exercise decreased aggressive behaviors by 68% Exercise alone more effective than combination of exercise and lorazepam in reducing aggression	Optimal exercise frequency unclear Did not control for fatigue as possible confounding factor in reducing aggression Staff needed to be present to conduct exercise sessions safely Unblinded outcome assessors
Wong et al. (1991)[91]	Autistic disorder (DSM-III-R[20]) Moderate ID 31 y.o. man	Poking, hitting, kicking others in state mental hospital; forcefully slapping own head (required 1:1 continuous observation and frequent application of seclusion or restraints)	A-B (quasi-experimental with extended follow-up)	DRO schedule: Reinforcement (e.g., candy) provided following certain interval of time during which target behavior (aggression) did not occur; beginning with short DRO intervals, gradually lengthening such intervals to encourage longer periods of appropriate behavior	Dramatic reduction in aggressive behavior and need for physical restraints (restraint use decreased from 42 incidents during first 24 days to no restraint use between days 200 and 300)	Quasi-experimental design makes it difficult to exclude medication effects or changes in staff behavior as alternate explanations for results (i.e. time-varying confounding) Unblinded outcome assessors
Hittner (1994)[92]	Autistic disorder (DSM-III-R[20]) Severe ID (full scale IQ = 32)	Aggression toward staff (including object throwing and table	A-B (quasi-experimental, simple interrupted time series)	Imipramine (150 mg/day) + DRA-O for 5 months	Substantial reduction in frequency of aggressive behavior, along with	Because of need to apprise all clinical personnel of medication changes and side effects, was not

Table 2

Continued

Study	Diagnosis	Nature of aggression	Study design	Intervention	Outcome	Limitations
	25 y.o. man	flipping), property destruction			improvements in anxiety and depressed mood	possible to keep staff "blind" to treatment protocol; hence, expectancy effects may have influenced data collection Because of quasi-experimental (simple interrupted time series) design, alternate hypotheses for results (e.g., maturation) could not be discounted (i.e., time-varying confounding)
Kennedy (1994)[93]	Autism (DSM-III[19]) Moderate ID 20 y.o. man	Grabbing others during demand situations and alterations in scheduling; biting self	A-B-A	Altering antecedent conditions, specifically provision of social comments by instructor (in addition to task demands): In first phase, task demands related to increased levels of problem behavior, and instructor social comments related to increased levels of positive social affect In second phase, low frequencies of task demands were interspersed with high frequencies of social comments, with task demands then faded in across sessions In third phase, task demands introduced in same manner as first phase	Reduction in aggressive behavior: In third phase, task demands no longer associated with problem behavior (even in absence of social comments), suggesting that manipulating antecedent events can alter effects of task demands on aggressive behavior	Could not exclude negative reinforcement extinction (in which problem behavior is reduced by repeatedly presenting a task demand but not allowing student to escape via problem behavior) or effects of fading alone as explanation for reduction in aggression (i.e., time-varying confounding) Unblinded outcome assessors
Reese et al. (1998)[94]	Autistic disorder (DSM-III[19]) Moderate to severe ID 26 y.o. man	Hitting, kicking, throwing objects, making verbal and physical threats	Reversal design examining effects of different DRO intervals across environmental contexts on rates of aggressive behavior	Combination of DRO procedure, token fines, and prompted relaxation over 5-day periods across various contexts (e.g., individual instruction, leisure time, house jobs)	Initial reduction in aggressive behavior dependent on choosing shorter DRO interval, with shorter DRO intervals more effective during activities in which baseline aggression rates were high (e.g., house jobs)	Generalization to community settings with fewer (or no) staff may be difficult Unblinded outcome assessors

Table 2

Continued

Study	Diagnosis	Nature of aggression	Study design	Intervention	Outcome	Limitations
					Once shorter DRO intervals successful in reducing aggressive behavior, longer DRO intervals effective at maintaining reductions, for up to 6 months	
Adelinis & Hagopian (1999)[95]	Autistic disorder (DSM-IV[21]) Moderate ID 27 y.o. man	Hitting, biting, kicking, pulling hair of others	A-B-A-B	Interrupting aggressive behaviors with "do" request (e.g., "Sit in a chair") as opposed to "don't" request (e.g., "Don't lie on the floor")	Substantial reduction in occurrence of aggression, with "do" requests provided during 4 10-minute sessions	Specific mechanism responsible for maintaining aggressive behavior unclear; for example, was aggression functionally related to contingent access to interrupted activity (positive reinforcement), contingent termination of "don't" requests (negative reinforcement), or combination of both Unblinded outcome assessors
Kaplan et al. (2006)[96]	Subject 1: Autistic disorder (criteria unspecified) Profound ID 52 y.o. man	Verbal and physical aggression (not specified)	A-B-A	Occupational therapy using Snoezelen (multisensory environment) approach: Each subject participated in several sessions of occupational therapy using Snoezelen approach (30 minutes twice weekly), followed by several non-Snoezelen occupational therapy sessions, followed by return to several Snoezelen occupational therapy sessions	Slight but noticeable reduction in frequency of aggressive incidents in days following Snoezelen sessions compared with frequencies observed during baseline and non-Snoezelen phases, suggesting that multisensory environment approach may have carryover effects in treating aggressive behavior for some days following treatment sessions (both subjects)	Small number of subjects Limited range of functional bases for problem behaviors (e.g., escape and tangible reinforcement); unclear how intervention would affect individuals with, for example, attention as functional basis for aggression
	Subject 2: Autistic disorder (criteria unspecified) Profound ID 47 y.o. man	Biting others				
McKee et al. (2007)[97]	Subject 1: Autistic disorder (criteria unspecified) Moderate ID	Assaulting staff and co-patients, throwing objects (furniture), hitting windows	A-B-A-B	Access to multisensory environment (Snoezelen room) for 28 days, followed by withholding access to Snoezelen room, followed by access again for 28 days	Snoezelen room associated with no clear effect on aggressive behavior, although trend toward more prosocial behavior (e.g., making eye contact,	Small number of subjects One subject spent only 30 minutes (as opposed to 45 minutes for other 2 subjects) in Snoezelen room each session

Table 2

Continued

Study	Diagnosis	Nature of aggression	Study design	Intervention	Outcome	Limitations
	31 y.o. man				assisting staff, shaking hands) following Snoezelen intervention	Stimulus preference screening (finding out what elements of Snoezelen room most pleasurable and suitable for each subject and customizing sessions to maximize those elements) not done; such efforts may have increased carryover to non-Snoezelen environment Unblinded outcome assessors
	Subject 2: Autistic disorder (criteria unspecified) Moderate ID 32 y.o. man	Assaulting staff and co-patients, spitting	A-B-A-B	Access to multisensory environment (Snoezelen room) for 28 days, followed by withholding access to Snoezelen room, followed by access again for 28 days	Snoezelen room associated with increase in aggressive behavior, although trend toward more prosocial behavior (e.g., making eye contact, assisting staff, shaking hands) following Snoezelen intervention	
	Subject 3: Autistic disorder (criteria unspecified) Moderate ID 28 y.o. man	Assaulting staff and co-patients, throwing objects	A-B-A-B	Access to multisensory environment (Snoezelen room) for 28 days, followed by withholding access to Snoezelen room, followed by access again for 28 days	Snoezelen room associated with no clear effect on aggressive behavior, although trend toward more prosocial behavior (e.g., making eye contact, assisting staff, shaking hands) following Snoezelen intervention	
McClean et al. (2007)[56]	Autistic disorder (criteria unspecified) Likely ID (conversed using repetitive phrases of up to 6 words; could carry out 1-step requests) 22 y.o. man	Punching, slapping, kicking, pulling hair of others	A-B	Positive behavior support: Activity sampling; picture sequencing to improve predictability of daily events; reduction of unnecessary speech; offering requests using visual, 2-way choice format; escape training (e.g., prompting escape to room and prompting verbal communication "Too noisy"); antecedent control procedures (e.g., turning off television or radio after exiting room and removing unnecessary demands)	Reduction in frequency of aggressive behaviors to near-zero levels within first 2 months, with sustained improvement over 24 months	As positive behavioral support is multi-element, not possible to isolate effect of individual interventions, account for contribution of nonspecific therapeutic factors (e.g., staff-client rapport), or separate effects of behavioral interventions from effects of range of support systems (i.e., time-varying confounding) Unclear if outcome assessors blinded
Flood et al. (2010)[98]	Autistic disorder (unspecified criteria) ID (unspecified severity;	Hitting, kicking, scratching, biting, grabbing; throwing objects at staff or peers; biting self to point of tissue	Reversal design examining effects of six different foods on aggressive behavior	Dietary intervention: 6 different foods were sequentially added and removed from diet to determine impact on aggressive behavior	No notable change in aggressive or self-injurious behavior (in either positive or negative direction)	Staff responsible for recording problem behaviors also prepared subject's meals during food evaluation phases and

Table 2

Continued

Study	Diagnosis	Nature of aggression	Study design	Intervention	Outcome	Limitations
	nonverbal subject) 21 y.o. man	damage on hands and arms				therefore were not blind to food conditions
McClean & Grey (2012)[57]	Autistic disorder (DSM-IV[21]) Severe ID 2 men (21 y.o and 23 y.o.)	Punching, kicking, hair pulling	A-B (quasi-experimental, multiple baseline across individuals design with extended follow-up)	Positive behavioral support-based, five-intervention sequence: Low arousal intervention, rapport building, visual scheduling, functionally equivalent skills teaching, and differential reinforcement strategies	Substantial reductions in aggressive behavior during low-arousal intervention phase, with further reductions noted during rapport-building and subsequent intervention phases; intervention gains maintained at 76, 104, and 152 weeks	Concomitant interventions with unknown effect occurred at most intervention phases—for example, access to certain foods (time-varying confounding) Order of interventions did not vary; therefore, cannot exclude order effects on outcomes Unclear if outcome assessors blinded
Guercio & Cormier (2015)[99]	ASD (DSM-5[1]) 23 y.o. man	Aggressive behavior, self-injury, property destruction whenever prompted to ride in van to day program	A-B-A-B	Task analysis/ forward-chaining approach combined with prompt stimulus fading: Specifically, task analysis used to construct series of 10 steps for transporting subject to day program; forward-chaining approach then used, in which completion of successive steps in transport rewarded by providing subject viewing time of favorite video Fading consisted of gradual reduction in number of staff (with whom subject was comfortable) joining subject in van on transport to point that only 1 staff needed for ride	Aggressive incidents decreased to zero during van rides, with only 1 staff required for ride	While task analysis/ chaining and prompt fading were effective in teaching new behavior, unable to determine contributions of each separate intervention Unblinded outcome assessors

ASD, autism spectrum disorder; DRA-O, Differential Reinforcement of Alternative and Other Appropriate Behavior; DRO, Differential Reinforcement of Other Behavior; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ID, intellectual disability; IQ, intelligence quotient; y.o., year old.

Table 3

Prospective Open Trials of Treatments for Aggression in Adults with Autism Spectrum Disorder

Study	Diagnosis	Subjects (number, sex, mean age)	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
Ratey et al. (1987)[100]	Autistic disorder (DSM-III[19])	n = 8 7 male, 1 female 32 years	Assaults on staff (not specified, except biting in 1 female subject)	Propranolol at average dose of 225 mg/day for 4 weeks	Staff report	Low HR and low BP at doses higher than 420 mg/day (1 subject) Unspecified adverse effects in another subject eventually necessitating discontinuation of medication	Substantial reduction in aggressive and impulsive behavior in all 8 subjects as reported by hospital staff Improvements in repetitive behavior, attention span, social skills over 4–5 months
Kuperman & Stewart (1987)[101]	Infantile autism (DSM-III[19])	n = 3 Unclear sex ratio of subjects with ASD Unclear mean age	Physically aggressive behavior (not specified)	Propranolol at mean dose of 166 mg/day	Parent, teacher, and physician report	No serious adverse effects reported A few subjects reported tiredness that resolved within few weeks	Reduction in aggressive incidents as observed and reported by parents, teachers, and treating physicians in 10 of 16 subjects However, unclear how many of responders were those with ASD
King & Davanzo (1996)[102]	Pervasive developmental disorder (DSM-III-R[20]) ID (severe in 2 subjects, profound in 5 subjects)	n = 7 adults with ASD and aggression as target symptom 3 male, 4 female 44.86 years	Aggression (not specified)	Buspirone at doses ranging from 30 to 60 mg/day for periods ranging from 58 to 289 days	Residential staff recording of frequency and severity of aggressive incidents	Unclear	Buspirone associated with worsening of frequency and severity of aggression in subjects with ASD compared to those without ASD
Hellings et al. (1996)[103]	Autistic disorder (DSM-III-R[20]) ID (borderline in 1, mild in 3, moderate in 3, severe in 2)	n = 9 total (5 adults with ASD) Unclear sex distribution among subjects with ASD Unclear mean age of subjects with ASD	Aggressive and self-injurious behavior (not specified)	Sertraline 25–150 mg/day for average of 109 days	CGI-S[35]	Agitation and skin picking in 1 subject at 50 mg/day who dropped out after 18 weeks	Substantial improvement in CGI-S[35] ratings in 8 of 9 subjects (mean improvement = 2.44) However, unclear how many of the 5 patients with ASD benefited from sertraline in terms of

Table 3

Continued

Study	Diagnosis	Subjects (number, sex, mean age)	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
							improvement in aggressive behavior
Brodkin et al. (1997)[104]	Autistic disorder (DSM-IV;[21] 18 subjects) Asperger disorder (DSM-IV;[21] 6 subjects) PDD NOS (DSM-IV;[21] 11 subjects)	n = 35 24 male, 11 female 30.2 years	Aggression (including destruction of property) and self-injurious behavior (not specified)	Clomipramine at average dose of 131 mg/day for 12 weeks	Brown Aggression Scale[34]	Seizures (3 subjects, 2 of whom had preexisting seizure disorder being treated with carbamazepine)	Significant reduction in subjects' scores on Brown Aggression Scale[34] (from average = 10.6 pretreatment to average = 3.7 posttreatment), including self-injurious behavior and destruction of property
Connor et al. (1997)[41]	Autistic disorder (DSM-III-R[20]) ID (profound)	n = 12 total (1 adult with ASD) 1 male with ASD 24 years	Physical assaults, verbal threats of violence, self-injurious behavior, explosive property destruction among sample as a whole; unclear whether the 1 adult with ASD was being treated for aggression or for inattention/ overactivity	Nadolol at mean dose of 109 mg/day for average of 11 weeks	Overt Aggression Scale[40]	Insomnia, sedation, nausea, and nightmares were the most commonly reported side effects among all 12 subjects	Significant reduction in Overt Aggression Scale[40] scores for the 10 subjects with aggression ($F[2,18] = 5.43$; $p < .05$) However, unclear from study whether the 1 adult with ASD was among the subjects with aggressive behavior or among those with inattention/ overactivity as target behavior
Horrigan & Barnhill (1997)[105]	Autistic disorder (DSM-III-R[20]) ID (borderline in 1, moderate in 1, severe in 3)	n = 5 5 male 27.8 years	Aggression (including hitting, kicking, biting) and self-injurious behavior (head banging, self-biting)	Risperidone at mean dose of 1 mg/day for 4 weeks	Conners APTQ[36]	Mild, initial sedation (2 subjects) Weight gain (from 1.27 to 3.64 kg) in all 5 subjects	Significant improvement (reduction) in aggression as reflected by improved Conners APTQ[36] scores (with changes ranging from −8 to −17 points) in all 5 adult subjects

Table 3

Continued

Study	Diagnosis	Subjects (number, sex, mean age)	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
Cohen et al. (1998)[106]	Autistic disorder (DSM-IV;[21] 2 subjects) PDD NOS (DSM-IV;[21] 1 subject)	n = 3 2 male, 1 female 38 years	Physical assaults, self-injurious behavior	Risperidone 3–6 mg daily for 3 months	Aggression monitored by direct care staff who "remained relatively consistent," although no interrater reliability established, and no specific instruments/scales used to measure aggression	Sedation (2 subjects) Akathisia (2 subjects) Pedal edema (1 subject, though this subject was also taking divalproex, which could have accounted for edema)	Substantial decrease in aggressive behavior in 2 of 3 subjects
McDougle et al. (1998)[46]	Autistic disorder (DSM-IV;[21] 22 subjects) Asperger's disorder (DSM-IV;[21] 6 subjects) PDD NOS (DSM-IV;[21] 14 subjects) All diagnoses aided by ADI-R[24] and ADOS[25]	n = 42 27 male, 15 female 26.1 years	Aggression, self-injurious behavior, and property destruction (not specified)	Sertraline 50–200 mg (mean = 122 mg) daily for 9 weeks	SIB-Q[46] CGI-I[35]	Weight gain (3 subjects) and anxiety/agitation (2 subjects) were the most commonly reported side effects	57% response rate (24 of 42 subjects) in terms of aggression, with response defined by CGI-I[35] posttreatment rating of "much improved" or "very much improved" Within DSM-IV[21] diagnostic subtypes, 68% (15 of 22) subjects with autistic disorder, 0% (0 of 6) subjects with Asperger's disorder, and 64% (9 of 14) subjects with PDD NOS were responders; lack of apparent response in subjects with Asperger's disorder possibly due to lower baseline severity of difficulties in this subgroup
Dartnall et al. (1999)[107]	Autistic disorder (DSM-IV;[21] 2 subjects)	n = 2 1 male, 1 female (separately studied)	Subject 1: Aggression toward others and the	Risperidone up to 3 mg/day (unspecified time interval)	Aggression recorded by residential staff with half-hour interval "spoilage"	No major adverse effects	Dramatic improvement in aggressive and self-injurious

Table 3

Continued

Study	Diagnosis	Subjects (number, sex, mean age)	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
	ID (both subjects profound)	30 years and 24 years, respectively	environment (e.g., head-butting others, suddenly and violently clearing items off tables)		or sampling technique in which waking hours divided into half-hour intervals, with interval marked "spoiled" if target behavior occurred one or more times during interval		behaviors, with maintenance of gains for 24 months
			Subject 2: Grabbing others	Risperidone up to 4 mg/day for 2 months	Aggression recorded by residential staff with half-hour interval "spoilage" or sampling technique in which waking hours divided into half-hour intervals, with interval marked "spoiled" if target behavior occurred one or more times during interval	40-pound weight gain over first year and unilateral gynecomastia	Virtual elimination of aggression and other target behaviors, with maintenance of gains over 34 months
Potenza et al. (1999)[47]	Autistic disorder (DSM-IV;[21] 5 subjects) PDD NOS (DSM-IV;[21] 3 subjects) All diagnoses aided by ADI-R[24] and ADOS[25]	n = 8 (4 adults with ASD) 3 male, 1 female 20.9 years	Aggressive behavior (unspecified)	Olanzapine 5–20 mg daily (mean = 7.8 mg daily) for 10 weeks (with a 2-week introductory period of 2.5 mg daily for all subjects)	SIB-Q[46] Visual Analog Scale[51]	Weight gain (6 subjects) Sedation (3 subjects)	Significant reduction in aggressive behavior in 6 of 7 subjects who completed study, as measured by changes in SIB-Q[46] scores (mean = 55.38 pretreatment to mean = 19.75 posttreatment) and by reductions in clinician ratings of "aggressive" on the Visual Analog Scale[51] over time (mean = 46.25 pretreatment to mean = 7.50 posttreatment)

Table 3

Continued

Study	Diagnosis	Subjects (number, sex, mean age)	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
							Positive effects first observable at end of 4th week of treatment However, unclear how many of 6 responders were adults
Rossi et al. (1999)[108]	Autistic disorder (DSM-IV[21])	n = 25 23 male, 2 female 9 years (range = 2 to 20); unclear how many adults)	Aggression toward others (not specified)	Niaprazine 1 mg/kg/day for 60 days	Behavioral Summarized Scale for Autistic Disorder[33]	Moderate daytime drowsiness in a few subjects	Significant reduction in Behavioral Summarized Scale for Autistic Disorder[33] scores in 52% of subjects ($p < .05$) after 60 days on number of dimensions, including aggression toward others However, unclear how many responders were adults
Fava & Strauss (2009)[109]	ASD (unclear which criteria used, but subjects had been diagnosed with autism per authors) ID (all subjects profound)	n = 27 (9 adults with ASD) Unclear sex distribution 37.8 years	Aggressive behavior (hitting, overturning furniture, spitting, threatening others)	2 different multisensory rooms (Snoezelen and stimulus preference rooms) for 25 minutes 3 times a week for 7 weeks	Target behaviors recorded by 3 "blind" observers (who did not know purpose of study and were not familiar with subjects) consisting of 2 occupational therapists and 1 behavioral psychologist	None reported	Frequency of aggressive behaviors decreased significantly ($F = 35.361$; $p = .00014$) after treatment only for individuals with ASD who attended Snoezelen condition, whereas stimulus preference condition effective in reducing disruptive behaviors only in individuals with profound ID without ASD
Miyaoka et al. (2011)[110]	Asperger's disorder (DSM-IV;[2] number of adult subjects unclear)	n = 40 subjects (unclear how many adults)	Aggression, self-injurious behavior, tantrums (not specified)	Yokukansan (TJ-54) at dose of 2.5–7.5 grams daily (mean =	CGI-I[35] ABC[30] (30% reduction in score)	Well tolerated; no subjects exited study due to adverse events	Response (as measured by ratings of "much improved" or "very much

Table 3

Continued

Study	Diagnosis	Subjects (number, sex, mean age)	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
	PDD NOS (DSM-IV;[21] number of adult subjects unclear)	Unclear sex ratio 15.6 years (range = 12 to 22 years)		6.2 grams daily) for 14 weeks			improved" on CGI-I[35] and 30% reduction in ABC[30] score) in 36 of 40 subjects (90%) in terms of aggression, self-injury, and tantrums However, unclear how many of 40 subjects were adults, and how many adults were considered responders
Miyaoka et al. (2012)[58]	Aspergers disorder (DSM-IV;[21] number of adult subjects unclear) PDD NOS (DSM-IV;[21] number of adult subjects unclear)	n = 40 subjects (unclear how many adults) 22 male, 18 female 22.7 years (range = 8 to 40 years)	Aggression, self-injurious behavior, tantrums (not specified)	Yokukansan (TJ-54) at dose of 2.5–7.5 grams daily (mean = 6.4 grams daily) for 14 weeks	CGI-S[35] (final score of 1 or 2) ABC-I[30] (80% or greater improvement)	Well tolerated; no subjects exited study due to adverse events	Response (as measured by final score of 1 [normal, not at all ill] or 2 [borderline mentally ill] on CGI-S[35] and 80% reduction in ABC-I[30] score) in 36 of 40 subjects (90%) in terms of aggression, self-injury, and tantrums However, unclear how many of 40 subjects were adults, and how many adults were considered responders
Stigler et al. (2012)[111]	Autistic disorder (DSM-IV-TR;[22] 25 adolescent and young adult subjects; number of adult subjects unclear)	n = 25 subjects (unclear how many adults) 21 male, 4 female 15.3 years (range = 12 to 21 years)	Severe tantrums, aggression, self-injury (not specified)	Paliperidone 3–12 mg daily (average = 7.1 mg daily) for 8 weeks	CGI-S[35] ABC-I[30] VABS Maladaptive Behavior Subscales[49] (secondary measure of irritability/ aggression)	Increased appetite, weight gain (average = 2.2 kg), sedation, and rhinitis	Significant treatment response in 21 of 25 subjects (84%) as measured by CGI-I[35] score of "much improved" or "very much improved" and

Table 3

Continued

Study	Diagnosis	Subjects (number, sex, mean age)	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
							≥25% improvement on ABC-I[30] subscale score (mean = 30.3 pretreatment to mean = 12.6 posttreatment), with specific improvements in realms of severe tantrums, aggression, and self-injury Significant improvement also noted on VABS Maladaptive Behavior Subscales,[49] with mean total scores decreasing from 37.4 to 25.1 ($p \leq .001$); all subjects with prior ineffective response to risperidone for irritability/aggression responded to paliperidone However, unclear how many adults in study, and of these, how many were responders

ABC, Aberrant Behavior Checklist; ABC-I, Aberrant Behavior Checklist–Irritability Subscale; ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; BP, blood pressure; CGI-I/S, Clinical Global Impression Scale–Improvement/Severity; Conners APTQ, Conners Abbreviated Parent-Teacher Questionnaire; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; HR, heart rate; ID, intellectual disability; PDD NOS, pervasive developmental disorder not otherwise specified; PANSS, Positive and Negative Symptom Scale; SIB-Q, Self-Injurious Behavior Questionnaire; VABS, Vineland Adaptive Behavior Scale.

adults (mean age = 22.7 years) with ASD, the use of blinded outcome assessors afforded this study a low risk of bias involving measurement of outcomes. The study was deemed to be at serious risk of bias, however, due to baseline or time-varying confounding, in that opportunities for socialization that the every-two-week visits may have conferred were not adequately measured or controlled for. Moreover, it is unclear from the study how many of the 40 subjects were adults and how many of the adult subjects were considered responders to yokukansan.

The Brodkin and colleagues[104] study showing beneficial effects of clomipramine on aggression in 18 of 33 (55%) adults with ASD was one of two prospective, open trials assessed to be at moderate (as opposed to serious) risk of bias due to baseline or time-varying confounding, as most subjects were on no other medications at the time of the study, subjects had minimal comorbid diagnoses, and a one-way analysis of variance (ANOVA) was used to assess the effect of time. Like most of the other studies, however, its lack of blinded outcome assessment conferred a serious risk of bias involving outcome measurement.

The McDougle, Brodkin, and colleagues[46] study demonstrating reduction in aggression in 24 of 42 (57%) adult subjects with ASD using sertraline was the other prospective, open trial assessed to be at moderate (as opposed to serious) risk of bias due to baseline or time-varying confounding, as a four-week washout of previously prescribed medications was performed, subjects with comorbid diagnoses other than intellectual disability were excluded, and an analysis of variance (ANOVA) was used to adjust for the effects of time and intellectual disability. Unblinded outcome assessment, however, bestowed a serious risk of bias involving outcome measurement, like most of the other trials in this category.

Overall, within the constraints imposed by the above limitations, evidence from prospective, open trials provides preliminary support for multisensory environments, yokukansan, clomipramine, and sertraline, among other interventions, in addressing aggressive behavior in adults with ASD. The uncontrolled, open nature of these trials, however, makes it difficult to conclude that the interventions studied were responsible for the effects observed, and to exclude other factors that could have accounted for the outcomes. Moreover, six of the studies[47,58,101,108,110,111] included a combination of adults and children, with lack of clarity as to how many adults were considered responders to the intervention in question. Randomized, controlled trials in adults would allow better determination of the efficacy of these approaches.

Retrospective Reviews

Table 4 summarizes the 8 retrospective reviews[39,112–118] that were examined regarding treatments for aggression in adults with ASD. Demographic information for the samples in each study (including sex distribution and mean age) are included in the table. These reports suggest potential utility of fluvoxamine,[114] clozapine,[115,117] ziprasidone,[39] aripiprazole,[116] quetiapine,[113] and antipsychotic combinations.[118]

As shown in Supplemental Table 2, http://links.lww.com/HRP/A138, all of these studies were assessed to be at low risk of bias with regard to selection of participants, misclassification of interventions, and deviation from intended interventions, and to be at moderate risk of bias involving selective reporting. All but one of the studies were judged to be at low risk of bias for missing data; the Wink and colleagues[118] study was assessed to be at moderate risk of bias in this domain because CGI-S[35] and CGI-I[35] outcome data were available only for a subset of patients in that study. All of the studies were judged to be at serious risk of bias due to baseline or time-varying confounding and measurement of outcomes, in line with the nature of retrospective reviews.

Overall, the uncontrolled nature of these studies makes it difficult to conclude that the interventions referenced were responsible for the effects observed, and the small sample sizes of these studies makes generalizability of the findings difficult. Nevertheless, many of the interventions referenced may warrant further controlled study.

Naturalistic, Case-Control Studies

One naturalistic, case control study[119] examined the treatment of aggression in adults with ASD.

Mehl-Madrona and colleagues[119] conducted a naturalistic, case-control study comparing micronutrient treatment with psychotropic medication in treating aggression, self-injurious behavior, and tantrums in individuals with ASD; 3 of 44 individuals in the micronutrient group and 7 of 44 in the medication group were adults. Medications used in the medication group included antipsychotics, selective serotonin reuptake inhibitors, stimulants, and beta blockers. The two groups were matched in terms of age, sex, IQ, family income, number of medications taken at study entry, and caretaker education. Both interventions were found to be associated with significant decreases in total ABC[30] scores, but the micronutrient group showed a significantly greater reduction in ABC[30] scores post-intervention compared to the medication group ($p < .0001$), including on the irritability subscale. In addition, the micronutrient group demonstrated a significant improvement on the CGI-I[35] compared to the medication group ($p = .0029$), with the latter showing no significant improvement. The most common adverse effects in the micronutrient group were anxiety, diarrhea, and nausea, whereas the most common side effects in the medication group were increased appetite, fatigue, and drowsiness. This study was judged to be at low risk of bias with regard to misclassification of interventions and deviation from intended interventions, and to be at moderate risk of bias regarding selective reporting. It was assessed to be at serious risk of bias, however, regarding selection of participants into the study (selection of participants into the study was related to intervention and outcome because the first author selected participants "after he realized that patients with ASD treated with both types of interventions seemed to have

Table 4

Retrospective Reviews of Treatments for Aggression in Adults with Autism Spectrum Disorder

Study	Diagnosis	Subjects (number, sex, mean age	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
Hollander et al. (2001)[112]	Autistic disorder (DSM-IV;[21] 10 subjects) Asperger's disorder (DSM-IV;[21] 2 subjects) PDD NOS (DSM-IV;[21] 2 subjects) IQ range, 20–105, mean = 69.1	n = 14 12 male, 2 female 17.93 years (range, 5–40 years) 4 adults (3 male, 1 female)	Aggression, self-injurious behavior, impulsivity (not specified)	Divalproex sodium 500–2500 mg daily (with blood levels from 65 to 92 µg/ml) for 2 to 27 months, depending on subject	CGI-I[35]	Hair loss, weight gain, sedation, buccal numbness (1 subject) Elevated liver enzymes (1 subject) Difficulty waking in morning (1 subject)	Substantial improvement (reflected by score of "much improved" or "very much improved" on CGI-I[35]) in 2 of 4 adult subjects (50%) in terms of overall clinical status; however, only 1 of 4 adult subjects actually demonstrated improvement in aggression 2 of other 4 subjects showed no improvement in these domains Another subject showed improvement in self-injurious behavior and impulsivity In both subjects with positive response, mood lability significantly improved
Corson et al. (2004)[113]	Autistic disorder (DSM-IV[21]) and severe ID (1 adult subject) Autistic disorder (DSM-IV[21]) and mild ID (1 adult subject) PDD NOS (DSM-IV[21]) and mild ID (1 adult subject)	n = 3 1 male, 2 female 25.67 years	Aggression (not specified)	Quetiapine 25–500 mg daily for 32 to 54 weeks	CGI-I[35] CGI-S[35]	Weight gain (2 of 3 adult subjects)	Modest effect on aggression Only 1 of 3 subjects had improved CGI-I[35] score ("much improved") pre- to post-treatment For entire sample (children + adults) of 20 subjects, CGI-S[35] scores changed from mean of 5.1 ("markedly ill") pre-quetiapine to mean of 4.2 ("moderately ill") post-quetiapine
Cohen et al. (2004)[39]	Autistic disorder (DSM-IV[21]) ID (profound in 9; borderline	n = 10 6 male, 4 female 43.8 years	Assault (n = 5), self-injury (n = 5), agitation (n = 3),	Ziprasidone at mean dose of 128 mg daily for 6 months (of note, 80% of subjects were	Maladaptive Behavior Scale[39]	No concerning side effects of ziprasidone noted	Improvement in Maladaptive Behavior Scale[39] scores in 6 of 10 patients (60%),

Table 4

Continued

Study	Diagnosis	Subjects (number, sex, mean age	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
	intellectual functioning in 1)		aggression (n = 1) (details not specified)	previously treated with risperidone)		80% of ziprasidone-treated patients lost weight (average = 9.5 pounds), 80% had decrease in cholesterol, and 60% showed decrease in triglycerides	compared to 6 months prior to ziprasidone treatment In 1 of 10 patients (10%), scores remained same, and in 3 of 10 patients (30%) scores worsened
Janowsky et al. (2005)[114]	Autistic disorder (DSM-III-R[20] or DSM-IV[21])	n = 8 6 male, 2 female 40.25 years	Aggressive behavior toward others (including hitting, biting, kicking, shoving), self-injurious behavior (including self-hitting, self-biting, head banging, cutting one's skin, skin picking), destructive behaviors (including overturning or breaking furniture)	Fluvoxamine 12.5–200 mg daily (5 subjects), paroxetine 10–40 mg daily (2 subjects), sertraline up to 200 mg daily (1 subject) for at least 6 weeks	Psychologist ratings of frequency of aggressive, self-injurious, and destructive behaviors based on staff observation Retrospective global behavioral ratings by one of authors roughly paralleling Severity of Illness component of CGI[35]	Overall well tolerated, although 1 subject experienced activation of target symptoms (e.g., aggression) on fluoxetine Weight gain in 7 subjects, but unclear how many of these had ASD	Significant reduction in ratings of aggressive, self-injurious, and destructive behavior, with maintenance of gains over 6-month period
Beherec et al. (2011)[115]	Autistic disorder (DSM-IV-TR;[22] 3 subjects) PDD NOS (DSM-IV-TR;[22] 3 subjects) All diagnoses corroborated by ADI-R[24] and ADOS[25]	n = 6 2 male, 4 female 23.2 years	Aggressive behavior (assaulting others, destroying property, self-injury)	Clozapine for 4 to 6 months (dose unspecified)	For each subject, proportion of days with aggression was measured during 4–6 months preceding initiation of clozapine and during 4–6 months following clozapine	Weight gain in most subjects, with average weight increase of 14.3 kg Constipation (5 subjects) Metabolic syndrome (1 subject) Tachycardia (1 subject) No patients developed agranulocytosis or	Proportion of days with aggression decreased from average of 19.1% during period preceding clozapine treatment to average of 10.7% during period following clozapine initiation (approximately 2-fold decrease) Reduction in number of antipsychotic medications used and in total antipsychotic dose

Table 4

Continued

Study	Diagnosis	Subjects (number, sex, mean age	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
					initiation, based on daily behavioral reports completed by nursing staff	extrapyramidal symptoms	from pre- to post-clozapine initiation
Ishitobi et al. (2012)[116]	Autistic disorder (DSM-IV-TR;[22] 16 subjects) Asperger's disorder (DSM-IV-TR;[22] 3 subjects) PDD NOS (DSM-IV-TR;[22] 4 subjects)	n = 23 16 male, 7 female 15.1 years (range, 9–24 years; unclear how many adult subjects)	Aggression (not specified)	Aripiprazole at mean dose of 2.8 mg daily for average of 14.9 weeks (after being switched from risperidone due to tolerability issues, including increased appetite and weight, hyperprolactinemia, somnolence, amenorrhea)	CGI-S[35] CGI-I[35]	Improvements in excessive appetite/weight gain in 7 of 11 patients (64%) who had experienced this side effect on risperidone Improvement in hyperprolactinemia in 3 male subjects	Aripiprazole at mean dose of 2.8 mg/day as effective as risperidone at mean dose of 0.7 mg/day at treating aggression and impulsivity (mean CGI-S[35] scores pre- and post-aripiprazole were 4.7 ± 1.4 and 4.6 ± 1.3, respectively; mean CGI-I[35] score was 3.4 ± 0.8), suggesting efficacy of risperidone for treating behavioral problems was maintained by aripiprazole Aripiprazole associated with improvements in excessive appetite/weight gain in 7 of the 11 patients (63.6 %) who had experienced this side effect on risperidone, and with improvement in hyperprolactinemia in 3 male subjects
Sajith (2017)[117]	ASD (unclear which criteria used, but subjects were admitted to specialist inpatient unit for adults with ID and autism	n = 3 All male 25.67 years	Aggression (destroying property, assaulting others, poking others' eyes, severe self-injurious behavior)	Clozapine 400–550 mg/day for 2 months	Staff observation of frequency of aggressive incidents	Tachycardia, drooling, and sweating (1 patient), which improved over time Transient sedation and constipation (1 patient)	Substantial reduction in frequency of aggression for all 3 patients

Table 4

Continued

Study	Diagnosis	Subjects (number, sex, mean age	Nature of aggression	Intervention	Measure of aggression	Adverse effects	Outcome
	associated with severe behavioral problems)					Generalized tonic-clonic seizure treated with levetiracetam and dose reduction of clozapine to 400 mg/day, with no further seizure recurrence (1 patient) No instances of neutropenia or agranulocytosis	
Wink et al. (2017)[118]	Autistic disorder (DSM-IV-TR;[22] 44 subjects) Asperger's disorder (DSM-IV-TR;[22] 3 subjects) PDD NOS (DSM-IV-TR;[22] 14 subjects) ID (41 subjects)	n = 61 53 male, 8 female 15.1 years (range, 4.2–26 years); unclear how many adults	Physical aggression (82%), self-injury (23%)	Daily doses of 2 or more antipsychotics concurrently for at least 2 clinic visits; most common initial combinations were risperidone + quetiapine (10 subjects), risperidone + aripiprazole (9 subjects), and aripiprazole + quetiapine (7 subjects); most common combinations at final visit were risperidone + quetiapine (10 subjects), aripiprazole + quetiapine (8 subjects), and risperidone + aripiprazole (5 subjects)	CGI-S[35] CGI-I[35]	Weight gain and sedation most common	Antipsychotic combinations found to be associated with small, nonsignificant reductions in agitation/irritability, aggression, and self-injury, reflected by modest decrease in CGI-S[35] scores from pre- to postintervention (mean = 4.7 pretreatment to mean = 4.6 posttreatment; p = .45) and mildly improved CGI-I[35] scores pre- to posttreatment

ADI-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; CGI-I/S, Clinical Global Impression Scale–Improvement/Severity; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ID, intellectual disability; IQ, intelligence quotient; PDD NOS, pervasive developmental disorder not otherwise specified.

done quite well, and he was curious enough to compare the data,"[119(p 101)] and this selection was not controlled for in analyses). The study was also judged to be at serious risk of bias involving baseline or time-varying confounding (there was no control over either intervention group's use of other resources or interventions, and there may have been differences between the families who sought micronutrient interventions and those who sought medication interventions), missing data (8 patients with ASD who received micronutrient interventions were excluded from the study due to incomplete outcome data, and the proportions of missing participants differed substantially across interventions), and measurement of outcomes (the clinician who conducted the chart review was not blinded). Moreover, the study included a small number of adults, limiting its power to detect differences between adults in the two groups. Overall, while the study suggests potential benefit of micronutrient interventions for aggression in individuals with ASD, its limitations portend caution in interpreting the results, particularly as applied to adults with ASD.

Randomized, Controlled Trials

Table 5 summarizes the 7 randomized, controlled trials[48,120–125] that were reviewed regarding treatments for aggression in adults with ASD. Demographic and other information for the samples in each study (including mean age, sex distribution, intellectual functioning, and verbal/nonverbal status) are included in the table. These trials explored the efficacy of vigorous aerobic exercise,[120] fluvoxamine,[121] risperidone,[48,122] vibroacoustic music,[123] transdermal nicotine,[124] and dextromethorphan/quinidine.[125]

As seen in Supplemental Table 3, http://links.lww.com/HRP/A139, all of the studies were judged to be at low risk of bias with regard to deviation from intended interventions (including effects of intervention assignment or adherence). All but one of the studies[125] were judged to be at low risk of bias due to missing outcome data. In addition, all but one of the studies[48] were assessed to be at moderate risk of bias arising from the randomization process (due to no information being provided on allocation-sequence concealment). Five of the 7 studies[120,122–125] were judged to be at moderate risk of bias with regard to measurement of outcome; 3 of these studies[122,124,125] employed crossover designs, in which rater blinding may have been compromised due to subjects receiving the study drug at predictable stages, and side effects/response possibly being obvious to single raters. The other 2 of the 7 studies[48,121] were judged to be at low risk of bias with regard to measurement of outcome because in each study outcome assessors were blinded (i.e., unaware of the drug assignment). All studies were judged to be at moderate risk of bias with respect to selection of reported results, due to data not clearly being analyzed in accordance with a prespecified plan that was finalized before unblinded data were available for analysis, though results were unlikely to have been selected from multiple eligible outcome measurements or from multiple eligible analyses of the data.

In the Elliott and colleagues[120] study, vigorous aerobic exercise (defined as exercise elevating heart rates to above 130 beats per minute after 20 minutes) via use of a motorized treadmill at 4.0 miles per hour reduced aggression in one subject, reduced property destruction in one subject, decreased self-injurious behavior in another subject, and reduced maladaptive stereotypic behaviors (e.g., rocking, loud vocalizations, teeth grinding) in all subjects (6 total) with ASD, to a greater degree than general motor training activities (activities elevating heart rates to between 90 and 120 beats per minute after 20 minutes, such as riding an exercise bike, lifting weights, or walking on a treadmill at 2.0 miles per hour) and a non-exercise control condition (playing with board games, puzzles, and crafts). Limitations of the study included its small sample size (including only 2 adults with ASD and aggressive behavior) and inadequate addressing of the randomization process (allocation-sequence concealment), measurement of outcome, and selection of reported results, leading to a moderate risk of bias in these three realms.

In the McDougle and colleagues[121] study, fluvoxamine at a dose of 50 to 300 mg/day over 12 weeks was associated with a significant improvement in aggression, repetitive thoughts and behavior, and maladaptive behavior in 30 adults with ASD. As noted previously, although this study was assessed to be at low risk of bias regarding deviation from intended interventions, missing outcome data, and measurement of outcome, it was deemed at moderate risk of bias regarding the randomization process and selection of reported results.

In the McDougle, Holmes, and colleagues[48] study, risperidone at a dose of up to 6 mg daily over 12 weeks was associated with a significant reduction in aggression (8 of 14 risperidone-treated subjects) compared to placebo (0 of 16 placebo-treated subjects)—improvements that were also demonstrated in a 12-week open-label phase of the study, in which 15 of the prior placebo-treated subjects then received risperidone. In this study, randomization (achieved using a computer-generated list with adequate allocation concealment), deviation from intended interventions, missing outcome data, and outcome measurement were adequately addressed, though freedom from selective reporting was not, leading to one potential moderate source of bias. Regarding missing outcome data, while the authors used a last-observation-carried-forward, intent-to-treat method for the 6 subjects who completed only 4 weeks of double-blind treatment—which in and of itself does not correct for bias due to missing outcome data—the reported reasons for the missing outcome data did not differ between intervention groups, and these reasons provided no evidence that missingness in the outcome depended on its true value.

In the Hellings, Zarcone, and colleagues[122] study, risperidone significantly decreased aggression in 35 of 40 children and adults with intellectual disability. It is unclear from the study how many of the 36 subjects diagnosed with ASD were adults, but the mean age of the sample was 22 years. Side effects included sedation and gastrointestinal disturbance in 13

Table 5

Randomized, Controlled Trials of Treatments for Aggression in Adults with Autism Spectrum Disorder

Study	Diagnosis	Subjects (number, sex, mean age, FS IQ, verbal/ nonverbal)	Intervention	Measure of aggression	Adverse effects	Outcome	Limitations
Elliott et al. (1994)[120]	Autistic disorder (DSM-III-R[20]) Profound ID	n = 6 total 2 adult females with ASD and aggression 32.5 years Unclear FS IQ, but both subjects had profound ID and mental age of 5.1	Vigorous, antecedent aerobic exercise (defined as exercise elevating heart rate to above 130 beats per minute after 20 minutes) via use of motorized treadmill at 4.0 miles per hour	Behavioral observation	None reported	Significant reduction in number and frequency of aggressive incidents (1 subject) and in frequency of property destruction (1 subject)	Small sample size Inadequate random sequence generation Unclear allocation concealment Possible concern for selective reporting
McDougle et al. (1996)[121]	Autistic disorder (DSM-III-R,[20] ICD-10;[23] corroborated with ADI-R[24] and ADOS[25])	n = 30 27 male, 3 female 30.1 years Mean FS IQ = 79.9 26 verbal, 4 nonverbal	Fluvoxamine 50–300 mg/day for 12 weeks	BAS[34]	Moderate sedation (2 subjects) Nausea (3 subjects)	Significant improvement in aggressive behavior as measured by changes in BAS[34] scores compared to placebo group ($F = 4.57$; $p < .03$)	Inadequate random sequence generation Unclear allocation concealment Possible concern for selective reporting
McDougle et al. (1998)[48]	Autistic disorder (DSM-IV;[21] 17 subjects) PDD NOS (DSM-IV;[21] 14 subjects) Corroborated with ADI-R[24] and ADOS[25]	n = 31 22 male, 9 female 28.1 years Mean FS IQ=54.6 15 verbal, 16 nonverbal	Risperidone up to 6 mg/day for 12 weeks	SIB-Q[46]	Sedation (8 subjects), weight gain (2 subjects), enuresis (2 subjects) were most common side effects in double-blind phase of study	Significant reduction in aggression compared to placebo, as measured by changes in total SIB-Q[46] scores ($F_{3,84} = 6.51$; $p < .001$) Reduction in aggression (as reflected by changes in total SIB-Q[46] scores) in 12-week open-label phase, in which 15 subjects from prior placebo group then received risperidone ($F_{3,42} = 3.07$; $p < .05$)	Possible concern for selective reporting
Hellings et al. (2006)[122]	Autistic disorder (DSM-IV;[21] 28 subjects)	n = 40 total 19 adult subjects: 11 male, 8 female	Risperidone low (2 mg/day) or high (4–5 mg/day) dose for 4 weeks in randomized,	ABC-I[30]	Sedation and gastrointestinal disturbance (nausea and abdominal	Significant decrease in ABC-I[30] scores at both doses compared to placebo (e.g., for	Heterogeneous sample, making predictors of response challenging to assess

Table 5

Continued

Study	Diagnosis	Subjects (number, sex, mean age, FS IQ, verbal/ nonverbal)	Intervention	Measure of aggression	Adverse effects	Outcome	Limitations
	PDD NOS (DSM-IV;[21] 8 subjects) Unclear how many subjects diagnosed with ASD were adults	ID: 3 mild, 4 moderate, 6 severe, 6 profound Unclear how many adults were diagnosed with ASD	placebo-controlled, crossover design; followed by 24-week, open-label risperidone (dose adjusted as needed)		discomfort) in 13 subjects Akathisia in 2 adult subjects (leading to dropout from the study) Recurrent oculogyric crises in one adult subject (which resolved with dose reduction) Mean weight gain = 6.0 kg in adult subjects	adults, from 19.16 in first placebo phase to 11.15 in low-dose risperidone phase and to 13.31 in high-dose risperidone phase) 23 subjects (57.5%) showed 50% reduction in Irritability subscale score (full response) and 35 subjects (87.5%) showed 25% decrease Clinical gains (as measured by ABC-I[30] scores) maintained during 24-week open-label maintenance phase	due to small subgroups Cannot exclude compromising of rater blinding with crossover design since subjects received study drug at predictable stages, and drug response and side effects may have been recognizable to a single rater Inadequate random sequence generation Unclear allocation concealment Possible concern for selective reporting
Lundqvist et al. (2009)[123]	Autistic disorder (DSM-IV;[21] 10 subjects) ID (DSM-IV;[21] 20 subjects)	n = 20 13 male, 7 female 37 years ID: 7 mild, 5 moderate, 8 severe 5 verbal, 15 nonverbal Unclear sex ratio, ID distribution, and verbal/ nonverbal ratio among the 10 subjects with ASD	10–20 minute sessions of vibroacoustic music twice weekly for 5 weeks (music therapy involving vibrations, delivered through specially designed speakers built into a chair, bed, or other equipment in order to administer low-frequency sound vibrations enabling listener to hear and physically feel the music)	Behavior Problems Inventory[31] Behavior observation analysis (in which video recordings of vibroacoustic music treatment sessions analyzed minute by minute with regard to type of behavior problem and frequency of behaviors)	None	Within ASD group, significant reduction in frequency and severity of self-injurious behavior ([$F_{(1,18)}$ = 5.02; p = .038], and [$F_{(1,18)}$ = 7.13; p = .016], respectively) Reduction in stereotypical and aggressive behavior in non-ASD group but not in ASD group	Small sample size Heterogeneity of problematic behaviors among subjects limited study power and raised error variance Inadequate random sequence generation Unclear allocation concealment Possible concern for selective reporting

Table 5

Continued

Study	Diagnosis	Subjects (number, sex, mean age, FS IQ, verbal/nonverbal)	Intervention	Measure of aggression	Adverse effects	Outcome	Limitations
Lewis et al. (2018)[124]	ASD (DSM-5;[1] unclear number of subjects) Autistic disorder (DSM-IV;[21] unclear number of subjects) Asperger's syndrome (DSM-IV;[21] unclear number of subjects) PDD NOS (DSM-IV;[21] unclear number of subjects)	n = 8 7 male, 1 female 24 years Mean FS IQ unclear Verbal/nonverbal status of subjects unclear	Transdermal nicotine 7 mg daily or placebo for 1 week, followed by 1-week washout period, during which all subjects received transdermal placebo, followed by 1 week of transdermal nicotine 7 mg daily or placebo, whichever was not received during first week	ABC-I[30]	Well tolerated, with no subjects dropping out of study due to side effects	In 5 subjects with available primary outcome data, mean ABC-I[30] scores decreased from baseline compared to placebo group, but difference was not significant (effect size = 0.49; p = .44) Significant correlation between improvement in ABC-I[30] and sleep with nicotine compared to placebo (r^2 = 0.89; p = .016)	Small sample size Short treatment period Questionable degree to which 7 mg dose of transdermal nicotine engaged α7 nAChR Cannot exclude compromising of rater blinding with crossover design since subjects received study drug at predictable stages, and drug response and side effects may have been recognizable to a single rater Inadequate random sequence generation Unclear allocation concealment Possible concern for selective reporting
Chez et al. (2018)[125]	Autistic disorder (DSM-IV-TR;[22] corroborated with ADOS[25])	n = 14 11 male, 3 female 21.92 years Mean FS IQ = 56.70 Unclear verbal/nonverbal ratio	DM/Q or placebo for 8 weeks, then 4-week washout period, then opposite treatment for another 8 weeks, then another 4-week washout period	ABC-I[30]	No reported serious adverse effects	In the 12 subjects who completed the study, DM/Q associated with significant reduction in irritability and aggression as measured by changes in ABC-I,[30] with nearly 4-point difference in change scores between DM/Q and placebo ($F_{1,10}$ = 7.42; p = .021)	Relatively small sample size Possible bias due to missing outcome data (2 randomized subjects withdrew from study as result of behavioral deterioration and were not included in analysis) Cannot exclude compromising of rater blinding with crossover design since subjects received study drug at predictable stages,

Table 5
Continued

Study	Diagnosis	Subjects (number, sex, mean age, FS IQ, verbal/nonverbal)	Intervention	Measure of aggression	Adverse effects	Outcome	Limitations
							and drug response and side effects may have been recognizable to a single rater Inadequate random sequence generation Unclear allocation concealment Possible concern for selective reporting

ABC-I, Aberrant Behavior Checklist–Irritability subscale; ADI, Autism Diagnostic Interview; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; BAS, Brown Aggression Scale; DM/Q, dextromethorphan/quinidine; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; FS IQ, Full Scale Intelligence Quotient; ICD-10, *International Statistical Classification of Diseases and Related Health Problems*, 10th revision; ID, intellectual disability; IQ, intelligence quotient; α7 nAChR, alpha-7 nicotinic acetylcholine receptor; PDD NOS, pervasive developmental disorder not otherwise specified; SIB-Q, Self-Injurious Behavior Questionnaire.

subjects (leading 6 to withdraw from the study during the active drug phase; data from these 6 subjects were included in the efficacy analysis), akathisia in 2 adult subjects (leading to dropout from the active phase of the study; data from these 2 subjects were included in the efficacy analysis), recurrent oculogyric crises in one adult subject (that resolved with dose reduction), and a mean weight gain of 6.0 kg in the adult subjects. While this study was assessed to be at low risk of bias regarding deviation from intended interventions and missing outcome data, it was judged to be at moderate risk of bias regarding the randomization process, measurement of outcome, and selection of reported results. Regarding missing outcome data, while the study did not clearly specify how data from the 8 subjects who withdrew from the active phase of the study were used in the efficacy analysis (or at what specific time point of the active phase withdrawal occurred), the reported reasons for the missing outcome data provided no evidence that missingness in the outcome depended on its true value; the study was therefore deemed at low risk of bias in this domain.

In the Lundqvist and colleagues[123] study, vibroacoustic music (music therapy involving vibrations, delivered through specially designed speakers built into a chair, bed, or other equipment) in 10- to 20-minute sessions twice weekly over five weeks significantly reduced the frequency and severity of self-injurious behavior in 10 subjects with ASD, and significantly decreased stereotypical and aggressive behavior in 10 subjects without ASD. While the study was judged to be at low risk of bias regarding deviation from intended interventions and missing outcome data, it was assessed to be at moderate risk of bias regarding the randomization process, measurement of outcome, and selection of reported results. Another limitation of the study included the small number of subjects with ASD (10).

In the Lewis and colleagues[124] study, transdermal nicotine at a dose of 7 mg daily over one week in 5 adult subjects with ASD was associated with a decrease in mean ABC-I[30] scores from baseline compared to the placebo group, but the difference was not statistically significant. While the study was judged to be at low risk of bias regarding deviation from intended interventions and missing outcome data, it was assessed to be at moderate risk of bias regarding the randomization process, measurement of outcome, and selection of reported results. Regarding missing outcome data, although data from 3 of the 8 randomized subjects were excluded from the efficacy analysis, the reported reasons for the missing outcome data provided no evidence that missingness in the outcome depended on its true value. Other limitations of the study included the small sample size (8 subjects), short treatment duration (1 week), and questionable degree to which the 7 mg dose of transdermal nicotine engaged the α7 nicotinic acetylcholine receptor.

In the Chez and colleagues[125] study, dextromethorphan/quinidine (DM/Q) was associated with a significant reduction in irritability and aggression in 12 adult subjects with ASD. While the study was judged to be at low risk of bias regarding deviation from intended interventions, it was deemed at

moderate risk of bias involving the randomization process, measurement of outcome, and selection of reported results, and high risk of bias due to missing outcome data. Regarding these missing data, 2 of 14 randomized subjects withdrew from the study at 17 weeks due to behavioral deterioration; their data were not included in the analysis, and missingness in outcome in these cases could have been, and were likely, influenced by the outcome's true value (i.e., it is possible that dextromethorphan-quinidine was ineffective at reducing aggression in these two subjects or may have produced behavioral deterioration as an unintended effect).

Overall, randomized, controlled trials suggest a number of interventions that may be effective in treating aggression in adults with ASD. Taking into account the constraints imposed by the aforementioned limitations, evidence from these trials provides preliminary support for risperidone, fluvoxamine, vigorous aerobic exercise, and dextromethorphan-quinidine in addressing aggressive behavior in adults with ASD. Many of these studies are limited, however, by small sample sizes (which may limit the generalizability of the results)[120,123–125] and short treatment durations (which make it difficult to conclude durability of any observed intervention effects over time, or whether intervention effects may have become more pronounced over time).[120,123–125]

Replication of preliminary positive findings using larger sample sizes, while adequately addressing sources of bias, is needed to formulate more definitive conclusions about the effectiveness of these treatments in reducing aggression in adults with ASD. Moreover, additional randomized, controlled studies of nonpharmacologic interventions for adults with ASD and aggression are needed.

DISCUSSION

The strongest evidence base (from controlled trials) preliminarily suggests beneficial effects of risperidone, propranolol, fluvoxamine, vigorous aerobic exercise, and dextromethorphan/quinidine for treating aggression in adults with ASD. Among these interventions, risperidone's efficacy is supported by two randomized controlled trials,[48,122] three prospective open trials,[105–107] and three case studies (including a total of 7 subjects).[72–74] Dosages of risperidone ranging from 1 to 6 mg (average = 3 mg) daily appear to be effective in treating aggression in adults with ASD. The other referenced treatments each have one controlled trial supporting their efficacy, with additional support provided through prospective, open trial (propranolol),[100,101] N of 1 nonrandomized crossover (exercise),[90] and retrospective (fluvoxamine)[114] evidence. Dosages of propranolol ranging from 80 to 320 mg (average = 200 mg) daily appear to be effective in treating aggression in adults with ASD. Dosages of fluvoxamine ranging from 12.5 to 300 mg (average = 156 mg) daily seem to be effective in this regard. Dosages of dextromethorphan-quinidine ranged from 20 mg dextromethorphan/10 mg quinidine once daily to the same combination twice daily in the one randomized, controlled trial that examined this intervention.

Lower levels of evidence (e.g., nonrandomized N of 1 trials, prospective open trials, retrospective reviews) point to possible benefits, in adults with ASD and aggression, of behavioral interventions,[56,57,67,85–88,91–95,99] multisensory environments,[96,109] yokukansan,[58,110] clomipramine,[104] sertraline,[46,103] clozapine,[115,117] and aripiprazole.[76,77,82,116] Among these interventions, multisensory environments and yokukansan are slightly more supported based on risk-of-bias assessments. While the level of evidence for these approaches is less robust than for controlled trials, the adverse effects and long-term risks associated with many of these treatments (in particular, behavioral interventions and multisensory environments) are significantly more favorable. Additional randomized, controlled trials of nonpharmacologic and pharmacologic approaches using consistent methodology, larger sample sizes, and longer treatment durations, and that adequately address sources of bias, would be helpful in clarifying which treatments can reliably be considered evidence based in managing aggression in adults with ASD.

Possible Explanations for Findings

So why would risperidone, fluvoxamine, propranolol, dextromethorphan-quinidine, exercise, yokukansan, ABA-based behavioral interventions, and multisensory environments be effective in reducing aggression in adults with ASD? That is, how specifically do these interventions work to decrease aggressive behavior in this population? While a well-studied and established mechanism for the development of aggression in adults with ASD has yet to be elucidated, neurobiological, behavioral, and cognitive-emotional theories have been explored and used as the basis for investigating various interventions to address aggression in individuals with ASD.

A number of studies have examined possible mechanisms underlying the neurobiology of aggression and potential factors contributing to the neurobiology of ASD. Considering the neurobiology of aggression first, studies have shown that changes in regional volumes, metabolism/function, and connectivity within neural networks involving regions of the prefrontal cortex, orbitofrontal cortex, cingulate cortex, striatum, insula, amygdala, hippocampus, and hypothalamus are consistently implicated in the biology of aggression.[126] Gene × gene[127] and gene × environment[128] interactions may also be involved, as may epigenetic factors leading to modifications in gene expression (such as perturbed maternal care in the postnatal period, stressful life events, or substance use).[129] In addition, abnormalities within the serotonergic,[130–142] dopaminergic,[143–150] noradrenergic,[151–158] and glutamatergic[159–166] neurotransmitter systems have been implicated.

Regarding neurotransmitter abnormalities, in particular, association of aggression with the serotonin (5-hydroxytryptamine [5-HT]) system has been suggested by numerous studies. Some studies have noted a relationship between low levels of 5-hydroxyindoleacetic acid (5-HIAA, the main metabolite of 5-HT) in cerebrospinal fluid (CSF) and increased aggression.[130,132–134] A related study showed that depressed

patients with low levels of 5-HIAA in their CSF were more likely to attempt suicide and to do so by violent means compared to depressed patients with high CSF 5-HIAA levels.[135] It has been hypothesized that the association between aggression and low CSF 5-HIAA levels is specific to impulsive behavior. Supporting this suggestion, a study of 36 murderers and attempted murderers found that impulsive violent offenders had lower CSF 5-HIAA levels than those who premeditated their crimes,[136] and another study found that low CSF 5-HIAA was predominantly associated with high impulsivity.[137] Despite these findings, the research linking low CSF 5-HIAA levels with aggression has been criticized by some for employing small sample sizes and being unable to control for confounding factors such as comorbid psychopathology;[138] in addition, some studies have failed to replicate the association.[131] Other studies have found that a blunted prolactin response to challenge with fenfluramine (a 5-HT agonist)—thought to characterize presynaptic or postsynaptic 5-HT dysfunction—was associated with increased impulsive aggression in personality-disordered patients;[139,140] a history of childhood physical or sexual abuse may predispose to this association.[141] Other studies have revealed significantly decreased levels of the serotonin transporter (5-HT transporter [5-HTT])—localized in the presynaptic membrane and responsible for clearing 5-HT from the extracellular space in order to be recycled or degraded, thus modulating the intensity of 5-HT signaling—in the anterior cingulate cortex of individuals with impulsive aggression.[142] Still other studies have demonstrated that specific mutations in the serotonin transporter gene resulting in lower expression and function of 5-HTT (and thus lower 5-HT reuptake activity) appear to be related to emotion dysregulation, including aggression.[126] Overall, the above findings implicating involvement of the serotonergic system in the neurobiology of aggression provide a theoretical rationale for using agents that modulate this system, such as selective serotonin reuptake inhibitors (e.g., fluvoxamine,[114,121] sertraline[46,103]), partial 5-HT1A agonists (e.g., yokukansan[58,110]), and partial 5-HT2A antagonists (yokukansan,[58,110] risperidone[48,72–74,105–107,122]) in treating aggression in adults with ASD.

The dopamine (DA) system, in addition to movement control, mediates positive emotionality, goal-directed behavior, and behavioral control related to reward expectancies.[143,144] Because of its role in governing reward-related behaviors and motivation processes, dysregulation of the DA system may promote pathological behaviors, including aggression.[126,145] Moreover, a specific mutation in the gene for catechol-O-methyl transferase (COMT), a major enzyme responsible for catabolizing catecholamines including DA, has been shown to result in reduced efficiency of DA elimination, leading to increased stimulation of DA neural networks involved in regulating emotional arousal, affective decision making, impulsivity, and aggression, such as the limbic structures and prefrontal cortex;[146] a specific polymorphism of this mutation has been associated with high levels of aggressive behavior in healthy young subjects.[147] In addition, CSF levels of homovanillic acid, a DA metabolite, have been shown to be lower in impulsively aggressive violent offenders with antisocial personality disorder than in non-impulsively aggressive offenders with paranoid or passive-aggressive personality disorder.[136] Furthermore, animal studies have shown the dopaminergic system to play a critical role in modulating aggressive behavior, with DA being localized in brain regions involved in controlling such behavior; for example, in Syrian hamsters, aggression was highly correlated with changes in hypothalamic DA levels,[148] and D2 receptors mediated the behavioral changes.[149] Also, increases in tyrosine hydroxylase and DA transporter messenger RNA (ribonucleic acid) levels have been noted in the ventral tegmental area of "winner" mice compared with "losers" and controls after experiencing repeated agonistic confrontations.[150] Overall, these findings implicating involvement of the dopaminergic system in the neurobiology of aggression lend support to the potentially useful role of DA-modulating agents, such as risperidone,[48,72–74,105–107,122] aripiprazole,[76,77,82,116] olanzapine,[47] clozapine,[52,55,115,117] and yokukansan[58,110] (a partial D2 agonist) in treating aggression in adults with ASD. Of note, given the above evidence implicating the serotonergic system in aggression, the strong 5-HT2A antagonism effects of risperidone, in addition to its DA D2 antagonism effects, may explain why it may be particularly effective in treating aggression in this regard.

The noradrenergic system has been implicated in and targeted for intervention in degenerative diseases such as Alzheimer's disease and Parkinson's disease.[151] Because brain areas involved in aggressive behavior, such as the amygdala, hippocampus, hypothalamus, and different parts of the cortex, receive projections from the locus coeruleus—the main nucleus of noradrenergic neurons in the central nervous system (CNS)—it has been posited that altered function or loss of noradrenergic neurons in the locus coeruleus could affect aggressive behavior.[126] In one animal study, highly aggressive male mice were given intraventricular injections of 6-hydroxydopamine in order to destroy noradrenergic terminals in the brain, after which a significant inverse correlation was found between norepinephrine (NE) depletion and fighting (i.e., greater NE depletion correlated with less aggressive behavior).[152] In another animal study, maprotiline, a NE reuptake inhibitor, was found to induce aggression during dyadic social interactions in male mice.[153] In human studies, several case reports have noted propranolol, a post-synaptic beta-adrenergic receptor blocker, to be effective in reducing aggression in hostile individuals with schizophrenia[154] and in individuals displaying aggression after CNS lesions.[155] In addition, it has been hypothesized that behavioral problems (including aggression) in individuals with ASD may be due to these individuals experiencing a chronic state of hyperarousal, supported by electrophysiologic studies demonstrating abnormalities of fast, low-voltage activity in the resting state,[156] electroencephalographic (EEG) studies showing

hyperarousal to auditory stimulation,[157] and neurochemical studies showing a two-fold increase in plasma NE levels compared to controls in individuals with ASD.[158] Decreasing such arousal by the use of beta blockers such as propranolol may reduce the impetus for these individuals to act impulsively or in a ritualized fashion.[100] Overall, these findings implicating noradrenergic dysfunction in aggression provide a logical rationale why propranolol[41,89,100,101] may be effective in reducing aggression in adults with ASD.

The role of the glutamatergic system in aggressive behavior has been suggested by a number of animal and human studies. For example, an early study[159] found that glutamate microinfused into the hypothalamus of cats induced attack and flight behavior similar to that induced by electrical stimulation. Other animal studies have noted that N-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine (PCP), dizocilpine (MK-801), and memantine inhibit displays of aggression in mice, although only at doses that also produce ataxia.[160] In addition, GPI-5232, an inhibitor of the enzyme that converts N-acetylaspartylglutamate to N-acetylaspartate and glutamate, has been shown to dose-dependently lower aggression in highly aggressive mice,[161] and JNJ16259685, a selective antagonist of metabotropic glutamate type 1 (mGlu1) receptors, has been shown to extinguish or attenuate aggression in mice at several doses.[162] In terms of human studies, a meta-analysis of three six-month, randomized studies noted that in individuals with Alzheimer's disease, treatment with memantine, a low-potency noncompetitive NMDA receptor antagonist, led to significantly more subjects experiencing improvement in the agitation/aggression symptom cluster compared to treatment with placebo.[163] Studies of NMDA modulators in children with ASD, however, have shown limited effectiveness of these agents in treating irritability.[164–166] Nonetheless, these findings implicating involvement of the glutamatergic system in aggression shed light on why agents that counteract excessive glutamatergic activity—such as dextromethorphan-quinidine[125] (dextromethorphan being a noncompetitive NMDA receptor antagonist and quinidine serving to increase the bioavailability and half-life of dextromethorphan)—may be effective at countering aggression in ASD.

Turning from the neurobiology of aggression to the neurobiology of ASD, studies in individuals with ASD suggest structural and functional abnormalities involving the prefrontal cortex,[167] frontal and temporal cortices,[168,169] limbic system (including the amygdala, hippocampus, and anterior cingulate),[170] striatum,[167,171] cerebellum,[172] and interconnections between these areas as contributory to many of the symptoms of this disorder. In addition, abnormalities in neurotransmitter synthesis, levels, or transporter binding (including serotonin,[173,174] dopamine,[175] norepinephrine,[176] glutamate,[173] and gamma-amino-butyric acid [GABA][173]), reduced expression/levels of neurotrophic factors,[177,178] increased oxidative stress,[179,180] and dysregulated hypothalamic-pituitary-adrenal (HPA) axis function[181,182] have been implicated in the neurobiology of ASD, with some of these factors (e.g., neurotrophin levels) likely moderating the above structural and functional brain region abnormalities.

Available data indicate that the neurobiology of physical exercise is characterized by modulatory effects on CNS neurotransmitters (including serotonin, dopamine, and norepinephrine),[183,184] neurotrophic factors,[185,186] functional connectivity within higher-level cognitive networks (e.g., including those involving the prefrontal cortex and orbitofrontal cortex),[187,188] the HPA axis,[189–191] and oxidative stress,[192–195] resulting in increased neurogenesis, angiogenesis, synaptogenesis, ability to manage stress, and neuronal resilience. Hence, by modulating neurotransmitter levels and function, inducing the increased expression of neurotrophic factors found to be deficient in many individuals with ASD, improving functional connectivity in higher cognitive networks implicated in ASD and in aggression, tempering HPA-axis function, and reducing oxidative stress, exercise may help to reduce aggression in individuals with ASD. The involvement of the serotonin, dopamine, norepinephrine, and glutamatergic neurotransmitter systems in the neurobiology of ASD also provides a plausible basis for explaining why serotonergic agents, dopamine-modulating agents, beta-adrenergic blockers, and anti-glutamatergic agents may be effective in treating aggression in adults with ASD. Moreover, while the neurobiological correlates of behavioral interventions in ASD have received limited study, preliminary evidence[196] suggests that ABA-based behavioral interventions such as pivotal response training in individuals with ASD may be associated with identifiable changes (e.g., increased activation) in brain areas such as the ventrolateral prefrontal cortex and superior temporal sulcus—areas associated with perspective taking and understanding the intentions of others—that may be relevant to the development of aggressive behavior in adults with ASD (see discussion under cognitive-emotional theories of aggression in ASD below).

Behavioral theories posit that aggression in individuals with ASD serves some function (e.g., to receive attention, escape from tasks or demands, obtain a tangible reinforcer, seek sensations/novelty) that leads to consequences that reinforce such behavior.[57,94,99] These behaviors are often triggered by some type of antecedent. For example, a young woman with ASD, in response to being instructed or reminded to take a shower by a caregiver (antecedent), may begin to scream and hit the caregiver (behavior), leading the caregiver to withdraw the shower reminder and offer an alternate, more desired activity (consequence). In this case, the individual's aggression effectively serves to provide an escape from the task/demand of taking a shower, and leads to receipt of a tangible reinforcer (more desired activity), prompting the individual to repeat this behavior each time she is asked to shower (positive reinforcement of aggressive behavior by providing a reward that increases behavior frequency; negative reinforcement of aggressive behavior by removal of undesired stimulus/demand of taking a shower). Another example would be a man with ASD who frequently punches holes in walls when feeling "bored" (antecedent), prompting

aggressive property destruction (behavior) that produces immediate gratification from the novel sensation of penetrating plaster/drywall (consequence). In this case, the aggression effectively serves to produce a reinforcing novel sensation that subsequently increases the frequency of the aggressive behavior. Behavioral interventions would therefore, in theory, reduce aggression in adults with ASD by providing positive reinforcement of desired behaviors and by minimizing unintentional (positive or negative) reinforcement of undesired behaviors. Thus, provision of frequent, meaningful, tangible reinforcers (e.g., food, time with favorite staff) for desired behaviors (e.g., lack of aggression) while ignoring or providing neutral responses to undesired behaviors (aggression) is a key component of using DRO schedules;[91,94] integrating social comments with task demands (and thus manipulating antecedent conditions) is a strategy employed in behavioral interventions designed to minimize the need to "escape" from such demands;[93] and allowing individuals with ASD the opportunity to engage in multisensory environments provides an attempt to address sensation-seeking bases for aggressive behavior.[96,109]

Cognitive-emotional theories of aggression in ASD contend that aggressive behavior in these individuals is the result of a combination of deficits in social cognition (including theory of mind, or the capacity to understand and appreciate others' mental states, and empathy) and emotion regulation.[53,197–199] Interventions aimed at addressing these deficits would therefore theoretically help to reduce aggression in adults with ASD. For example, Stichter and colleagues[200] developed a group-based social competence intervention, based on cognitive-behavioral therapy (CBT) principles, to target deficits in theory of mind, emotion recognition, and executive function in 27 students aged 11 to 14 with ASD. Program elements included skill instruction, modeling, and practice in structured and naturalistic settings, with specific focus on facial-expression recognition, sharing ideas with others, turn taking in conversations, recognizing feelings/emotions of self and others, and problem solving. Significant improvement was noted on direct assessments of theory of mind, facial-expression recognition, and problem solving, as well as on parent-reported social skills and executive functioning in all students. While the study was conducted in adolescents, it may be a potentially useful intervention in adults with ASD, warranting further study.

Researchers have also explored the utility of dialectical behavior therapy to improve emotion regulation in individuals with intellectual disabilities, some of whom were diagnosed with ASD.[201–203] This research has examined various populations, including intellectually disabled adults living in supervised residential settings[201] and adult offenders.[202,203] These reports provide preliminary promise for dialectical behavior therapy as a helpful intervention to improve emotion-regulation strategies, and therefore potentially aggression, in individuals with ASD. Additionally, recent research has posited that a history of traumatic experiences may contribute to an increased risk of aggression in individuals with ASD, via deficits in theory of mind, executive function, and central coherence (the ability to form a coherent understanding of what is occurring by taking note of how context affects the meaning of what is said and done), affecting trauma processing in ways that portend aggression.[204] Interventions specifically for individuals with ASD who have experienced trauma would thus theoretically help reduce the risk for aggression in such individuals; studies in this arena have mostly focused on children but provide preliminary hope for CBT-based therapies, including trauma-focused CBT and CBT to treat anxiety and teach emotion regulation.[205]

In summary, by targeting systems implicated in the neurobiology of aggression or the neurobiology of ASD, interventions such as dopamine-modulating agents (e.g., risperidone), serotonergic agents (e.g., fluvoxamine, sertraline, yokukansan), beta-adrenergic blockers (e.g., propranolol), anti-glutamatergic agents (e.g., dextromethorphan-quinidine), and exercise may exert beneficial effects on aggression in adults with ASD. Behavioral theories contend that by facilitating positive reinforcement of desired behaviors (including lack of aggression), discouraging positive or negative reinforcement of aggressive behaviors, and accurately identifying the functional bases for aggression, behavioral interventions (such as ABA-based approaches and multisensory environments) may also help to reduce aggression in this population. Finally, cognitive-emotional theories of the basis for aggression in ASD imply that interventions that address social-cognitive deficits and emotion-regulation problems, as well as any history of psychological trauma, would help to decrease or prevent aggression in these individuals.

Limitations

While this review has attempted to synthesize the available scientific literature to identify evidence-based interventions for aggression in adults with ASD, some limitations are worth noting. First, the heterogeneity of study designs, sample sizes, subject presentations, treatment durations, interventions, and methods used to diagnose ASD or to measure aggression, as examined in this review, makes it difficult to draw firm conclusions about what particular treatments are most effective for aggression in adults with ASD. For example, as noted above, only 33 of the 70 studies reviewed used a standardized instrument to measure aggression, and among those, there was substantial variation in the assessments used; the lack of a standardized assessment across studies poses a limitation to drawing definitive conclusions in this review. Second, as noted earlier, only a minority of the reviewed studies (24 of 70) assessed subjects for comorbid psychiatric diagnoses, a factor that has been shown to be often associated with aggression in individuals with ASD.[53] Even among the studies that did assess this factor, only two controlled for comorbid psychiatric diagnoses in their analyses of study findings.[89,114] As noted earlier, although the presence of comorbid psychiatric diagnoses did not appear to have a substantial impact on response to interventions for aggression in this review, the number of studies assessing comorbidity (24 of 70) was

relatively small, and there are challenges in accurately assessing comorbidity in individuals with ASD.[63] Third, the number of randomized, controlled trials identified (seven in this review) was limited, and only two examined the same intervention (risperidone).[48,122] More controlled and comparative studies are needed to better answer the question of which treatments for aggression in adults with ASD are most effective. Fourth, while many of the behavioral interventions reviewed were deemed to be supported by lower levels of evidence (based on study designs being nonrandomized, unblinded, and uncontrolled), for many of these interventions, it was practically difficult to achieve blinding of study personnel because of the nature of behavioral interventions and because of the subjects residing in settings in which staff familiar with the subjects were most feasibly able to administer (with training), or to assess response to, such interventions (e.g., subjects may not have cooperated with interventions administered by unfamiliar research personnel, and residential/hospital staff who were present 24 hours a day were best able to document incidents of aggression). It may be that these

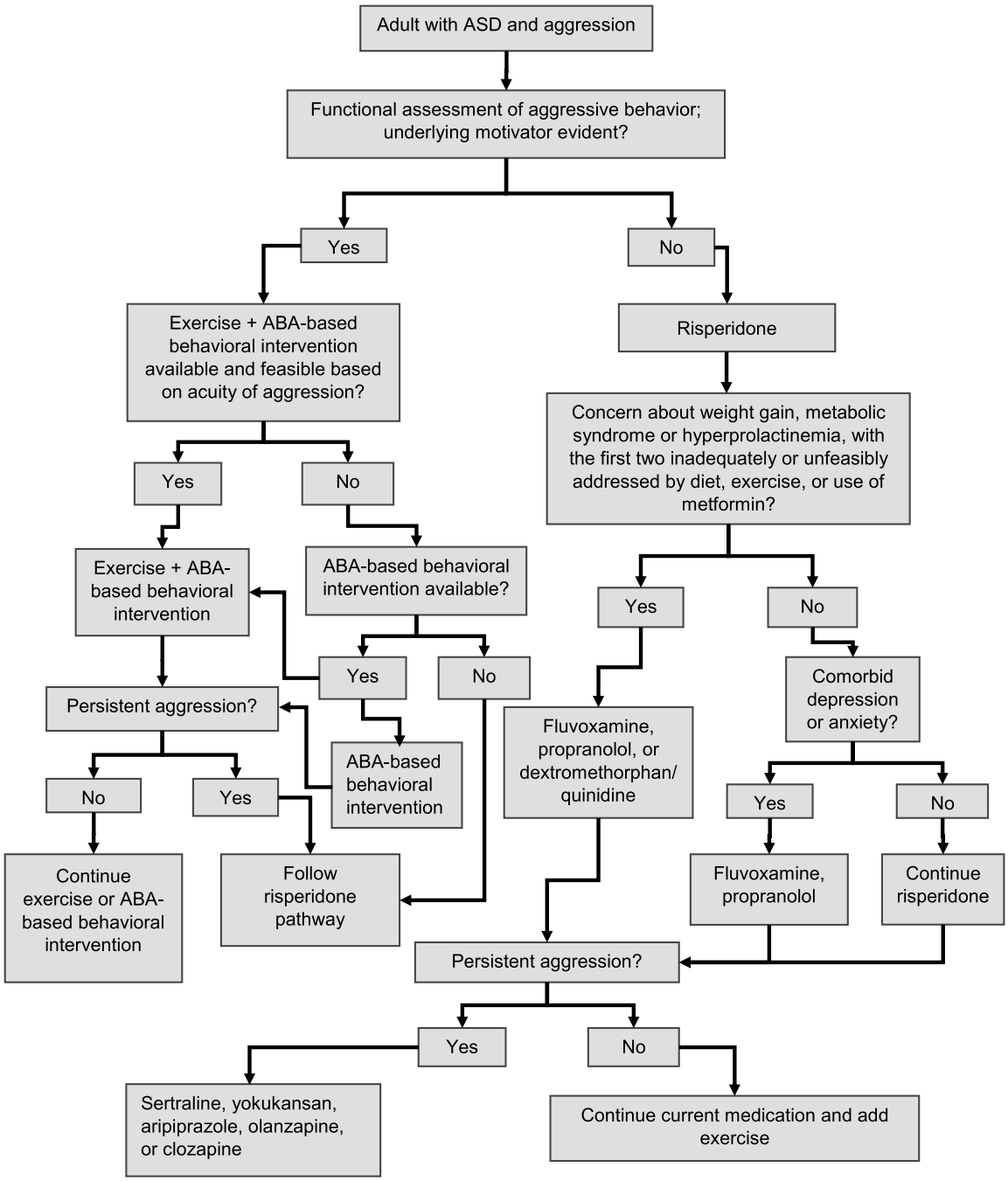

Figure 1. Schematic of one approach to managing aggression in adults with autism spectrum disorder. ABA, applied behavior analysis.

interventions are just as effective as, or more effective than, those supported by blinded, controlled studies, but that the constraints in question preclude such study designs. Use of the ROBINS-I tool[65] was an attempt to address some of these issues in comparatively evaluating study quality/risk of bias, albeit imperfectly. Finally, the vast majority of the reviewed studies focused on *treating* aggression in adults with ASD, with less emphasis placed on *preventing* aggression in this population. Longer-term, prospective studies would be helpful to determine if certain interventions (e.g., exercise) prove to have preventive, as well immediate therapeutic, value in addressing aggression in adults with ASD, particularly if the interventions are associated with minimal long-term risks.

Implications for Practice

Taking into account the available evidence base, the potential benefits and adverse effects/risks of specific interventions, and the preferences of individuals with ASD, the following approach could be considered in addressing aggressive behavior in adults with ASD (see Figure 1). First, consistent with recommendations by Matson and Jang,[5] a functional assessment of the behavior could be conducted to identify factors underlying the aggression (e.g., whether it is motivated by escape from task demands, desire for tangible reinforcers, stimulation/sensation seeking, attention seeking, or other factors). Once such factors are identified, a behavioral approach utilizing principles of applied behavior analysis could be used to target the aggression, given the minimal adverse effects and long-term risks associated with this approach (e.g., DRO schedule, positive behavioral support, non-exclusionary time out, forward chaining with stimulus fading, use of social comments prior to tasks, behavioral report card, token economies). If available, multisensory environments could also be employed at this stage, given their benign adverse-effect profile and open-trial evidence of efficacy[109] in adults with ASD. If such interventions are unavailable or ineffective, or if the acuity of the individual's aggression is too high to permit safe and effective implementation of these approaches, pharmacotherapy can be used, ideally after a discussion with the individual regarding the purpose, benefits, risks, and side effects of, and alternatives to, medication treatment, in an attempt to help the individual maintain some sense of autonomy/control despite the intensity of concern caused by his or her behavior.

Risperidone at a dose of 1 to 6 mg daily (average = 3 mg daily) would be a primary consideration in this context, based on the relatively greater number of controlled studies supporting its effectiveness in treating aggressive behavior in adults with ASD.[48,122] Starting with 1 mg at night, risperidone can be increased, if necessary, by 1 mg every two to three days to achieve therapeutic effect (reduction in aggression) up to a maximum of 6 mg daily if tolerated. If risperidone at an adequate dose (up to 6 mg daily, based on the reviewed studies) and with good tolerability fails to effectively reduce aggression in an adult with ASD, fluvoxamine, propranolol, or dextromethorphan-quinidine could next be considered, based on these agents having controlled evidence (albeit less than risperidone) in support of their efficacy for this purpose.[89,121,125] These same medications could also be considered if there is particular concern about weight gain, metabolic syndrome, or hyperprolactinemia with risperidone (in case the first two concerns are inadequately or unfeasibly addressable by diet, exercise, or use of metformin[206]); comorbid depression or anxiety could serve as additional reasons to specifically consider fluvoxamine or propranolol, respectively. Should the individual's aggression fail to show adequate improvement with these approaches, yokukansan or sertraline could next be considered, given their open-trial evidence of efficacy[46,58,103,110] and more benign metabolic profiles than antipsychotics. Should the aggression continue to show inadequate response, aripiprazole, clozapine, olanzapine, or ziprasidone could next be considered, with careful monitoring for adverse effects associated with these agents. If medication interventions are used, they should be prescribed, in line with prior recommendations,[4] at the lowest doses necessary to sufficiently address the individual's aggression, be monitored closely for adverse effects, and be reevaluated at regular intervals to determine if they are still necessary.

Finally, based on evidence from controlled[120] and N of 1 crossover[90] trials, and in light of the potential weight gain/metabolic side effects associated with many pharmacologic interventions, physical exercise could be strongly encouraged in adults with ASD presenting with aggressive behavior, ideally for at least 20 minutes three to four times weekly, at an intensity sufficient to achieve heart rates above 130 beats per minute. This may require the assistance of staff, depending on the level of functioning, cooperation, and motivation of the individual with ASD. In addition to a direct effect on aggression, as suggested by some studies,[120] and its physical health benefits, exercise may help with comorbid conditions, such as depression.[207] Along with ABA-based interventions, exercise, based on its favorable side-effect and long-term risk profiles, could be considered as an initial measure, with consideration of pharmacotherapy if exercise is unavailable, ineffective as a sole intervention, or infeasible given the severity of the aggression. Even if pharmacotherapy is employed, continuation of exercise as an adjunctive measure would be prudent to counteract medication-related metabolic side effects.

CONCLUSION

ASD is a neurodevelopmental disorder for which associated maladaptive behaviors such as aggression can significantly disrupt functioning and quality of life. Because most individuals with ASD will spend the majority of their lives as adults,[4,5] there is a compelling need for effective treatments for aggression in adults with ASD in order to minimize adverse outcomes (e.g., harm to others or to the individual with ASD,[2,6,7] hindering of educational or employment opportunities,[2,3] involvement with the criminal justice system[6–8]). This review has attempted to synthesize the available scientific literature to provide an updated summary of all

evidence-based interventions for aggression in adults with ASD. Based on the available evidence and consideration of adverse effects and long-term risks, a practical approach could involve behavioral interventions and exercise as an initial measure in addressing aggression in adults with ASD, whenever possible. If these interventions are unavailable or the severity of aggression precludes their safe implementation, pharmacotherapy (with risperidone as a primary consideration) can be employed, using the lowest possible dosages, with close monitoring for adverse effects, and with regular reevaluation of its need. If pharmacotherapy is utilized, adjunctive exercise is recommended to counteract possible metabolic side effects of medications. As more is learned about the genetic, neurobiological, environmental, and other determinants of aggressive behavior in adults with ASD, due diligence by the scientific community in examining a broad and innovative array of treatment approaches will be imperative to meet the needs of this vulnerable and underserved population.

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