Supplementary Table 1: Categories of evidence and strength of recommendations

Categories of evidence for causal relationships and treatment
Ia: Evidence from meta-analysis of randomised controlled trials

Ib: Evidence from at least one randomised controlled trial

IIa: Evidence from at least one controlled study without randomisation

IIb: Evidence from at least one other type of quasi-experimental study

III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies

IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Categories of evidence for observational relationships
I: Evidence from large, representative population samples

II: Evidence from small, well-designed, but not necessarily representative samples

III: Evidence from non-representative surveys, case reports

IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Strength of recommendation
A Directly based on category I evidence

B Directly based on category II evidence or extrapolated from category I evidence

C Directly based on category III evidence or extrapolated from category II evidence

D Directly based on category IV evidence or extrapolated from category III evidence

S Standard of good clinical care

Supplementary table 2: **DSM-5 diagnostic criteria for ASD**

A) Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive):

1 Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions.

2 Deficits in non-verbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and non-verbal communication;

to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and non-verbal communication.

3 Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers.

B) Restricted, repetitive patterns of behaviour, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive):

1 Stereotyped or repetitive motor movements, use of objects, or speech (eg, simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).

2 Insistence on sameness, inflexible adherence to routines, or ritualised patterns of verbal or non-verbal behavior (eg, extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day).

3 Highly restricted, fixated interests that are abnormal in intensity or focus (eg, strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).

4 Hyper- or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (eg, apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).

C) Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life).

D) Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.

E) These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level.

Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder.

Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder.

Specify if:
•With or without accompanying intellectual impairment
• With or without accompanying language impairment
• Associated with a known medical or genetic condition or environmental factor
• Associated with another neurodevelopmental, mental, or behavioural disorder
• With catatonia (refer to the criteria for catatonia associated with another mental disorder)

(***Reproduced from the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5))***

Supplementary table 3- Severity specifiers for the characterization of variation in adaptive functioning in autism spectrum

	Social communication	**Restricted, repetitive behaviours**
Level 3 **Requiring very substantial support**	Severe deficits in verbal and non-verbal social communication skills cause severe impairments in functioning, very limited initiation of social interactions, and minimal response to social overtures from others. For example, a person with few words of intelligible speech who rarely initiates interaction and, when he or she does, makes unusual approaches to meet needs only and responds to only very direct social approaches.	Inflexibility of behaviour, extreme difficulty coping with change, or other restricted/repetitive behaviours markedly interfere with functioning in all spheres. Great distress/ difficulty changing focus or action.
Level 2 **Requiring substantial support**	Marked deficits in verbal and non-verbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions; and reduced or abnormal responses to social overtures from others. For example, a person who speaks simple sentences, whose interaction is limited to narrow special interests, and who has markedly odd non-verbal communication.	Inflexibility of behaviour, difficulty coping with change or other restricted/repetitive behaviours appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress and/or difficulty changing focus or action.
Level 1 **Requiring support**	Without supports in place, deficits in social communication cause noticeable impairments. Difficulty initiating social	Inflexibility of behaviour causes significant interference with functioning in one or more contexts. Difficulty switching between

	interactions, and clear examples of atypical or unsuccessful response to social overtures from others. May appear to have decreased interest in social interactions. For example, a person who is able to speak in full sentences and engages in communication but whose to-and-fro conversation with others fails, and whose attempts to make friends are odd and typically unsuccessful.	activities. Problems of organisation and planning hamper independence.

(***Reproduced from the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5))***

Supplementary table- 4 Screening tools for children and young people

	Validity	Age	Description
Modified-Checklist for Autism in Toddlers (M-CHAT)	**Sensitivity:** 64% (18-48 months) 88%(30-48 months) **Specificity** 75%(18-48 months) 38% (30-48 months) (Charman et al., 2015)	16-30 months	23 item questionnaire by caregiver
Early Screening for Autistic Traits (ESAT)	Positive predictive value 25% for ASD (Dietz et al., 2006)	14 months	14 item 2-stage questionnaire completed by health practitioner after interview with caregiver
Checklist for		18 months	14 item 2 stage

Autism in Toddlers (CHAT)	Sensitivity 21% Specificity 100% Positive predictive value 59% **(**Baird et al., 2000)		questionnaire: 5 completed by health practitioner 9 completed by caregiver
Social Communication Questionnaire (SCQ)	a) Sensitivity 82%(18-48 months) Specificity 50%(18-48 months) (Charman et al., 2015) b) Sensitivity 56%(4-12yr old) 69%(13-21years old) c) Specificity 74%(4-12yr old) 71%(13-21years old) (Barnard-Brak et al., 2015)	> 4 years	40 item questionnaire completed by caregiver
Childhood Autism Spectrum Test (CAST)	Sensitivity 100% Specificity 97% (Williams et al., 2005)	4-11 years 10-16 years	50 item questionnaire completed by caregiver
Parents Evaluations for Developmental Status (PEDS)	**Sensitivity** 68%(21 months to 4.5 years) 87% (4.5 - 8 years) **Specificity** 66%(21 months to 4.5 years)	21 months to 8 years	18 item questionnaire 10 open –ended questions about behavior, learning and development 8 questions with prompts to parents for

	79%(4.5-8 years) (Glascoe, 2003)		each developmental domain
Screening Tool for Autism in Toddlers (STAT)	**Sensitivity** 92% (12-35 months) **Specificity** 85% (12-35 months) (Stone et al., 2004)	24-36 months	12 item questionnaire; 2 stages
Social Responsiveness Scale (SRS)	**Sensitivity** 75% **Specificity** 96% (Constantino et al., 2007)	>2.5 years	65 item questionnaire completed by caregiver
Autism Spectrum Screening Questionnaire (ASSQ)	**Sensitivity** Non clinical setting P: 91%, T: 90% Clinical Setting P: 62%, T: 70% **Specificity** Non clinical setting P: 77%, T: 58% Clinical Setting P: 90%, T: 91% (Ehlers et al., 1999)	7-16 years	27 item questionnaire completed by caregiver

Supplementary table 5- ***Diagnostic Instruments for children and young people***

	Validity	Age	Description
Autism Diagnostic Observation Schedule (ADOS)	Sensitivity 94-100% Specificity 52-76%	>12 months	Clinical observation via interaction

	(Zander et al., 2015)		
Autism Diagnostic Interview Revised (ADI-R)	**Sensitivity** 44-52% **Specificity** 91-96% (Zander et al., 2015)	>2 years	93 item interview with caregiver
Developmental, Dimensional, Diagnostic Interview (3Di)	**Sensitivity** 100% **Specificity** 98% (Skuse et al., 2004)	>2 years	266 item computer- based interview with caregiver
Diagnostic interview for Social Communication Disorders (DISCO)	Sensitivity 96% Specificity 79% (Maljaars et al., 2012)	All ages	362 item interview with caregiver
Development and Well Being Assessment (DAWBA)	Sensitivity 92% in the clinic sample Specificity 89% in the community sample (Goodman et al., 2000)	5-16 years 11-16 years	4 components i) Interview ii) Parent interview iii) Teacher questionnaire iv) Computer based rating
Childhood Autism Rating Scale (CARS)	Sensitivity 94% Specificity 85% (Perry et al., 2005)	>2years	15 item completed by researcher, and a questionnaire completed by caregiver

Supplementary table 6- Screening tools for Adults

	Validity	Age	Description
Autism Spectrum Quotient (AQ)	Sensitivity 95% Specificity 52% (Woodbury-Smith et al., 2005)	>16 years	50 item questionnaire; self-report
Social Responsiveness Scale (SRS-A)	**Sensitivity** Men: 84% Women: 95% **Specificity** Men: 81% Women: 61% (Takei et al., 2014)	>18 years	65 item questionnaire completed by caregiver
Ritvo Autism Asperger Diagnostic Scale-Revised (RAADS-R)	**English sample:** **Sensitivity:** 97% **Specificity:** 100% (Ritvo et al., 2011) **Swedish sample** **Sensitivity:** 91% **Specificity:** 93% (Andersen et al., 2011)	> 18years	80 item questionnaire; self-report

Supplementary table 7. Summary of treatment studies for core symptoms of ASD

Study	Design	Population	Age (years)	Sample size (total)	Drug and dose (final mean unless other stated)	Comparator	Duration (weeks)	Primary outcome	Secondary outcomes
Serotonergic agents									
Barthelemy et al (1989)	R, DB, PC	ASD	3-10	13	Fenfluramine 1.5 mg/kg	Placebo	12	None specified	Behavior Summarized Evaluation Scale↔
King et al (2009)	R, DB, PC	ASD	5-17	149	Citalopram 16.5 mg/day	Placebo	12	CGI-I↔	CYBOCS-PDD↔ RBS↔ ABC-I↑ ABC- other subscales↔
Hollander et al (2005)	R, DB, PC, XO	ASD	5-17	45	Fluoxetine 10 mg/day	Placebo	2 x8	CY-BOCS↑	CGI-AD↔
Neuropharm (2012) unpublished data	R, DB, PC	ASD	5-17	158	Fluoxetine 2-18 mg/day	Placebo	14	CYBOCS↔	
McDougle et al (1996)	R, DB, PC	ASD	18-53	30	Fluvoxamine Max of 300 mg/day	Placebo	12	CYBOCS↑	VABS↑ CGI-I↑ Brown Aggression Scale↑ RFRLS ↑
Buchsbaum et al (2001)	R, DB, PC, XO	ASD	30.5 (8.6)	6	Fluoxetine 20-40 mg/day	Placebo	16	None specified	CYBOCS↑ CGI-I ↔ Hamilton Anxiety ↑ Hamilton Depression ↔

Hollander et al (2012)	R, DB, PC	ASD	18-60	37	Fluoxetine 64.76mg/day	Placebo	12	Y-BOCS↑ CGI –I for obsessive compulsive scale↔	CGI-I↑ HAM-D↔ ABC-I↔
Glutamatergic agents									
Jacquemont et al (2011)	R, DB, PC	FXS	18-35	30	AFQ056 Dose was titrated up from day 1 to day 20 up to 150 mg twice a day and then down to 50 mg twice a day for the last four days of the trial	Placebo	4	ABC-C↔	ABC- L/SW↑ CGI ↔ VABS↑ RSR-R↑ VAS↑ SRS↑
Berry-Kravis et al (2016)	R, DB, PC	FXS	Adults: 18-45 Adolescents 12-17	175 adults 139 adolescents	AFQ056 25 mg -100mg twice a day	Placebo	12	ABC-C_{fx} ↔in FXS with complete mutation or partial mutation	CGI-I ↔ RSR-R↔ SRS↔ CNS-VS↔ TEA-CH↔
Erickson et al (2007)	OpL	PDD	6-19	18	Memantine 10.1 mg/day	None	19.3	None specified	CGI- S↑ CGI- I↑ ABC-H/NC↑ ABC-other subscales ↔
Aman et al (2017)	a) R, DB, PC b) OpL extension	ASD	6-12	a) 121 b) 104	Memantine 3-15 mg/day	Placebo	a) 12 b) 48	SRS↔	CATS-I↔ CCC-2↔

Posey et al (2004)	SB	PDD	5.1–27.6	12	d-cycloserine in three ascending doses (0.7, 1.4, and 2.8 mg/kg/day) doses were changed every 2 weeks	Placebo	8	None specified	CGI-S ↑ SRS↔ ABC- L/SW↑ ABC- other subscales↔ CY-BOCS↔
Minshawai et al (2016)	R, DB, PC	ASD	5-11	60	d-cycloserine 50 mg/day	Placebo	10	SRS↔	VABSII↔ ABC↔ CGI ↔ TSSA↔
Berry-Kravis et al (2006)	R, DB, PC	FXS	6-21	49	CX516 300mg/day	Placebo	4	Memory Sub- tests of the Test of Visual—Perceptual Skills↔	W-JR- Memory for words subtest ↔ RBANS↔ SNAP IV, and the Integrated Visual & Auditory Continuous Performance Test↔ Peabody Picture Vocabulary Test-III (Forms A and B) and the Preschool Language Scale–4 ↔ Clinical Evaluation of Language Fundamentals-3 ↔ ABC-I↑

									ABC- other subscales ↔ CGI-I↔
GABAergic agents									
Berry-Kravis et al (2012)	R, DB, PC, XO	FXS	6-39	63	Arbaclofen 20-30mg/day	Placebo	4	ABC-I↔	ABC-SA↑ in subgroup with severe social imp. ABC-L/SW↔ CGI↔ VAS↑
Erickson et al (2014)	OpL	ASD PDD PDD-NOS	6-17	32	Arbaclofen 2-30mg/day	N/A	8	ABC-I↑	ABC-L/SW↑ CGI-I↑ CGI-S↑ SRS↑ CY-BOCS-PDD↑ CASI↑ ADHD-A scale↑ VABS- Communication subscale↑
Veenstra-VanderWeele et al (2016)	R, DB, PC, XO	ASD	5-21	150	Arbaclofen Children = 26.8mg/day adults = 41.1mg/day	Placebo	12	ABC-L/SW↔	CGI -S↑ CGI-I↔ VAS ↔ VABS↔ ADHD-IV↔
Fung et al (2014)	OpL	ASD	22.5 (5.8)	12	Pregnenolone 50-250mg/day	N/A	12	ABC-I↑	ABC- L/SW↑ ABC-other subscales↔ SSP↔ SRS ↔

									VABS↔
Dopamine receptor blockers									
McDougle et al (2005)	Secondary analysis of McCracken (2002) and RUPPAN (2005)	ASD	8.8 (2.7)	101	Risperidone 2.0mg/day	Placebo	8 & 16	Primary outcomes are reported in McCracken et al (2002) and RUPPAN (2005)	RFRLS↑ Y-BOCS↑ VABS↑
Scahill et al (2013)	Secondary analysis of McCracken et al (2002) and Aman et al (2009)	ASD PDD	1)5-17 2) 4-13	225	Risperidone 0.5-3.5 mg/day	Placebo	8	None specified	↑ABC-L/SW

Marcus et al (2009)	R, DB, PC	ASD	6-17	218	Aripiprazole Randomised dose 5, 10, or 15 mg/day	Placebo	8	ABC-I↑	CGI-I↑ CYBOCS↑ ABC-SB↑ PedsQL↑
Owen et al (2009)	R, DB, PC	ASD	6-17	98	Aripiprazole Randomised dose 5, 10, or 15 mg/day	Placebo	8	ABC-I↑	CGI-I↑ CY-BOCS↑ ABC-SB↑ PedsQL↑
Aman et al (2010)	Line-item analysis based on the studies by Marcus et al (2009) and Owen et al (2009)	ASD	6-17	316	Aripiprazole Flexible: 2-15mg/day Fixed: 5, 10, 15mg/day)	Placebo	8	ABC-I↑	ABC-SB↑ ABC-H/NC↑ ABC-IS↑
Other agents									
Jahromi et al (2009)	Secondary analysis of RUPPAN	PDD ADHD	5-13	33	Methylphenidate 0.125, 0.25, 0.5 mg/kg BID	Placebo	4	joint attention and self-regulation behaviours that was dose-	

	(2005)							dependent.↑	
Anagnostou et al (2012)	R, DB, PC	ASD	18-60	19	Oxytocin Intranasal 24 IU twice a day	Placebo	6	CGI-I↔ DANVA-2↔ RBS-R↑ low order behaviors	Reading the mind in the eyes test↑ QoL↑ SRS↔ YBOCS↔ RBS-R high order behaviors↔
Watanabe et al (2015)	R, DB, PC	ASD	18-55	18	Oxytocin Intranasal 24 IU twice a day	Placebo	6	ADOS reciprocity↑	SRS↔ RBS↔ AQ↔ STAI↔ QoL↔ CGI↔ GAF↔
Guastella et al (2015)	R, DB, PC	ASD	12-18	50	Oxytocin Intranasal 18-24 IU twice a day	Placebo	18	SRS↔ RBS↔ RMET-A↔ RMET-C↔	DBC↔ RBS↔
Yatawara et al (2016)	R, DB, PC, XO	ASD	3-8	31	Oxytocin Intranasal 12 IU twice a day	Placebo	5	SRS-P↑ RBS-R ↔	CGI-I↑ ADOS- reciprocity↔ ADOS-communication↔ DBC-P↔ CSQ↔

R=randomized, DB=double blind, SB=single blind, PC=placebo-controlled, OpL= open-label, XO=cross over ↑= significant improvement ↔ no change
ABC = Aberrant Behavior Checklist, ABC-H/NC = ABC- Hyperactivity/Noncompliance, ABC-I = ABC Irritability, ABC-L/SW = ABC-Lethargy/Social Withdrawal, ABC-IS = ABC-Inappropriate Speech, ABC-SB = ABC-Stereotyped Behavior, ABC-SA = ABC-Social Avoidance, CATS-I = Core Autism Treatment Scale-Improvement (CATS-I), CCC-2 = Children's Communication Checklist-2, (C)Y-BOCS = (Children's) Yale-Brown Obsessive Compulsive Scale, IU = international unit, CSQ = caregiver strain questionnaire, DANVA-2 = Diagnostic Analysis of Nonverbal, Accuracy, ADOS = Autism Diagnostic Observation Schedule, RBS(-R) = Repetitive Behavior Scale(-Revised), DBC = Developmental Behavioural Checklist, GAF = Global Assessment of Functioning, CGI = Clinical Global Impression, STAI = State-Trait Anxiety Inventory, AQ = Autism Quotient, SRS = Social Responsiveness Scale, PedsQL = Pediatric Quality of Life Inventory, RFRLS = Ritvo-Freeman Real-Life Rating Scale, VABS = Vineland Adaptive Behaviour Scale, VAS = Visual Analogue Scale, TEA-CH = Test of Everyday Attention for Children, CNS-VS = computerized cognitive test battery CNS Vital Signs, W-JR = Woodcock-Johnson

Tests of Cognitive Ability—Revised, RBANS = The Repeatable Battery for the Assessment of the Neuropsychological Status, SNAP-IV = Swanson, Nolan and Pelham (SNAP) questionnaire.

Supplementary table 8. Summary of treatment studies for co-morbid conditions

Study	Design	Population	Age (years)	Sample size (total)	Drug and dose (final mean unless other stated)	Comparator	Duration (weeks)	Primary outcome	Secondary outcomes
Fankhauser et al (1992)	R, DB, PC, XO	ASD	5-33	9	Clonidine 0.005 mg/kg/day	Placebo	4	None specified	RFRLS-Sensory Motor↔ RFRLS-Affectual Reactions↑ RFRLS-Social Relationship↑ RFRLS-Language↔ RFRLS-Sensory Response↑ CGI↑
Jaselskis et al (1992)	R, DB, PC, XO	ASD	5-13	8	Clonidine 0.15-0.20mg/day	Placebo	6	None specified	ABC-I↑ ABC-L/SW↔ ABC-SB↑ ABC-H/NC↑ ABC-IS↑ CGI-I ↔ CPRS↑
Kent et al (2013)	R, DB, PC	ASD	9 (3.1)	96	Risperidone Low dose =0.125 - 0.175 mg/day High dose = 1.25 - 1.75 mg/day	Placebo	6	ABC-I ↑ (high dose)	ABC-H/NC ↑ (high dose) ABC-SB ↑ (low dose) CY-BOCS compulsions ↑ (high dose)
McDougle et al (2005)	Secondary analysis of McCracken (2002) and RUPPAN (2005)	ASD	8.8 (2.7)	101	Risperidone 2.0mg/day	Placebo	8 & 16	Primary outcomes are reported in McCracken et al (2002) and RUPPAN (2005)	RFRLS↑ Y-BOCS↑ VABS↑
Shea et al (2004)	R, DC, PC	ASD	7.5 (2.3)	79	Risperidone 1.17mg/day	Placebo	8	ABC-I ↑	ABC-H/NC↑ ABC-IS↑ ABC-L/SW↑ ABC-Stereotypy↑ N-CBRF (parent version): Conduct Problem↑ Hyperactive↑

									Self-isolation↔ Insecure/anxious↑ Overly Sensitive↑ Self-injurious/stereotypic↔ VAS (most troublesome symptom) ↑
Troost et al (2005)	OpL+ R,DB PDisc	ASD	9 (2.3)	26 (OpL) 24 (PDisc)	Risperidone 1.9mg/day	Placebo	8+16+8	Relapse rate↑	ABC-I↑ ABC-H/NC↔ ABC-IS↔ ABC-L/SW↔ ABC-SB↔
Gordon et al (1993)	R, DB, PC	ASD	10.4 (4.1)	24	Clomipramine 152mg/day	Placebo Desipramine = 127mg/day	10	CPRS – Autism Subscale↑ vs placebo & desipramine	CPRS OCD Subscale↑ vs placebo & desipramine CGI-efficacy index ↑ vs placebo & desipramine NIMH OCD Scale ↑ vs placebo & desipramine NIMH Global OCD Scale↑ vs placebo & desipramine NIMH Anxiety scale↑ vs placebo & desipramine
King et al (2009)	R, DB, PC	ASD	9.3 (3.1)	149	Citalopram 16.5mg/day	Placebo	12	CGI-I ↔	CYBOCS-PDD↔ RBS-R↔ ABC↔
Hollander et al (2012)	R, DB, PC, XO	ASD	34 (14)	37	Fluoxetine 64.76 mg/day	Placebo	12	Y-BOCS↑	CGI↑ ABC-I↔
Hollander et al (2005)	R, DC, PC, XO	ASD	8 (3)	45	Fluoxetine 9.9mg/day	Placebo	8	CY-BOCS-compulsions ↑	CGI-AD↔
Gringras et al (2012)	R, DB, PC, XO	Neurodevelopmental and neurological disorders	8.5 (3)	146	Melatonin .05-12mg/day	Placebo	12	Sleep time↑	Sleep onset↑
Cortesi et al (2012)	R, DB, PC	ASD	6.4 (1.1)	144	Melatonin 3mg/day	Placebo	12	Sleep time↑ drug alone and combination in combination	Sleep onset↑ Sleep efficiency ↑

					CBT four sessions of 50m with a clinical psychologist			with CBT	Wake after sleep onset↑ All alone and combination superior to placebo
Shea et al (2004)	R, DB, PC	ASD	7.5 (2.3)	79	Risperidone 1.17mg/day	Placebo	8	ABC-I↑	ABC-H/NC↑ ABC-IS↑ ABC-L/SW↑ ABC-SB↑ N-CBRF(PV) conduct problems↑ N-CBRF(PV) insecure/anxious↑ N-CBRF(PV) hyperactive↑ N-CBRF(PV) overly sensitive↑ CGI-C↑ VAS – most troublesome symptom↑
Kent et al (2013)	R, DB, PC	ASD	9 (3.1)	96	Risperidone low =0.125 -0.175 mg/day high = 1.25 -1.75 mg/day	Placebo	6	ABC-I↑ high dose	ABC-H/NC↑ high dose ABC-IS↔ ABC-L/SW↔ ABC-SB↑ low dose CGI-S↑ high dose CY-BOCS↑ high dose
McCracken et al (2002)	R, DB, PC	ASD	8.8 (2.7)	101	Risperidone 1.8mg/day	Placebo	8	ABC-I↑	ABC-H/NC↑ ABC-IS↔ ABC-L/SW↔ ABC-SB↑ CGI-I ↑
Luby et al (2006)	R, DB, PC	ASD	4 (1)	32	Risperidone 1.38mg/day	Placebo	26	CARS↑	
Nagaraj et al (2006)	R, DB, PC	ASD	5 (1.7)	40	Risperidone 1mg/day	Placebo	26	CARS↑	CGAS↑
Marcus et al., (2011)	OpL safety report follow-up of Marcus (2009) and Owen (2009)	ASD	9.6 (3)	330	Aripiprazole 10.6mg/day	N/A	52	Adverse events: Weight gain Vomiting Nasopharyngitis Increased appetite Pyrexia Upper respiratory tract	Discontinuation mostly due to aggression and weight increase.

								infection Insomnia	
Paribello et al (2010)	OpL	FSX	18 (5)	20	Minocycline 100 or 200mg/day	N/A	8	ABC-I↑	VAS for behaviour↑ CGI-I↑ ABC-L↔ ABC-SB↑ ABC-H↑ ABC-IS↑
Leigh et al., (2013)	R, DB, PC	FSX	9.2 (3.6)	55	Minocycline 25-100mg/day	Placebo	13	CGI-I↑	VAS – most troublesome symptom↔ ABC ↔ VABS-II ↔ EVT-2↔
Erickson et al., 2014	OpL	ASD	6-17	32	Arbaclofen 2-30mg/day	N/A	8	ABC-I↑	ABC-L/SW↑ ABC-H/NC↑ ABC-IS↔ ABC-SB↑ RRS↑ CY-BOCS-PDD↑ ADHD-IV RS↑ CGI-I↑ CGI-S↑
Veenstra-VanderWeele et al., 2016	R, DB, PC	ASD	11.6 (4.6)	150	Arbaclofen Children = 26.8mg/day adults = 41.1mg/day	Placebo	12	ABC-L/SW↔	CGI-S↑ CGI-I↔ ADHD-IV RS↔ VAS-Anxiety↔ VAS-Disruptive↔ VABS II Socialisation↔
Berry-Kravis et al., 2012	R, PC, DB, XO	FSX	6-40	63	Arbaclofen 20-30mg/day	Placebo	4	ABC–I↔	CGI-I↔ CGI-S↔ VAS Problem behaviours↑
King et al., 2001	R, DB, PC	ASD	5-11	39	Amantadine 5mg/kg per day	Placebo	4	Responder rate↔	ABC-I↔ ABC-L/SW↔ ABC-H/NC↑ ABC-IS↑ ABC-SB↔

									CGI↑
Reichow et al., 2013	Meta-analysis of four studies	ASD	7	94	Methylphenidate .4-.45mg/kg	Placebo	1-2	ADHD symptoms↑	Hyperactivity↑
RUPP, 2005	R, DB, PC, XO + OpL	ASD	7.5 (2.2)	72	Methylphenidate 7.5-50mg/day	Placebo	4 + 8 OpL	ABC-H/NC↑	ABC-I↔ ABC-L/SW↔ ABC-IS↑ ABC-SB↑
Harfterkamp et al., 2012	R, DB, PC	ASD	9.95 (2.8)	97	Atomoxetine 1.2mg/kg/day	Placebo	8	ADHD-RS↑	ADHD-RS Inattention↑ ADHD-RS Hyper-imp↑ CTRS-R:S Hyperactivity↑ CTRS-R:S Oppositional↔ CTRS-R:S Cognitive/attention↔ CTRS-R:S ADHD↔ CGI-I↔
Arnold et al., 2006	R, DB, PC, XO	ASD	9.26 (2.93)	16	Atomoxetine 20-100mg/day	Placebo	6	ABC-H/NC↑	Hyperactivity/impulsive↑ Inattentive↔ ABC-I↔ ABC-L/SW↑ ABC-IS↔ ABC-SB↔
Handen et al., 2015	R, DB*, PC + parent training (PT)	ASD	8.1 (2.1)	128	Atomoxetine 40-49.8mg/day 9 sessions of Parent Training (PT)	(1) ATX (2) ATX+PT (3)Placebo+PT (4)Placebo	10	SNAP-P ADHD↑ (1:4, 2:4, 3:4) HSQ↑ (1:4, 2:4)	ABC-H/NC↑ (1:4, 2:4) ABC-I↑ (3:4) ABC-L/SW↔ ABC-IS↑ (2:4, 3:4) ABC-SB↔ SSQ↑ (3:4) SNAP-P Inattention↑ (1:4, 2:4, 3:4) SNAP-P Hyperactivity↑ (1:4, 2:4, 3:4)
Smith et al 2016	DB**, PC extension to Handen 2015	ASD	8.1 (2.1)	117	Atomoxetine 49.8(23.3) alone 40.0(18.4) combined	ATX, ATX+PT, Placebo+PT, placebo	24	None specified	
Scahill et al. 2015	R, DB, PC	ASD	8.5 (2.25)	62	Guanfacine 1-4mg/day	Placebo	8	ABC-H/NC↑	ABC-I↑↓ ABC-L/SW↔ ABC-IS↑

									ABC-SB↑ ADHD-RS ↑ ADHD-RS Inattention↑ ADHD-RS Hyperactivity↑
Niederhofer et al., 2002	R, DB, PC, XO	ASD	8.3 (3.55)	12	Lofexidine 0.8-1.2mg/day	Placebo	6	None specified	CPRS↑ ABC-H/NC↑ ABC-I↑ ABC-SB↑ ABC-IS↑ Clinician ratings↔
Buchsbaum et al., 2001	R, DB, PC, XO	ASD	30.5 (8.6)	6	Fluoxetine 20-40mg/day	Placebo	16	None specified	Y-BOCS↑ Y-BOCS Obsessions↑ Y-BOCS Compulsions↔ CGI Autism ↔ Hamilton Anxiety↑ HRSD ↔
McDougle et al., 1998	R, DB, PC	ASD	28.1 (7.3)	31	Risperidone 2.9 mg/day	Placebo	12	None specified	CGI↑ Y-BOCS↑ SIB-Q↑ RFRLS-Sensory Motor↑ RFRLS-Affectual Reactions↑ RFRLS-Social Relationship↔ RFRLS-Language↔ RFRLS-Sensory Response↔
McDougle et al., 1996	R, DB, PC	ASD	30.1 (7.7)	30	Fluvoxamine 276.7mg/day	Placebo	12	Y-BOCS↑	CGI↑ VABS ↑ Brown Aggression Scale↑ RFRLS-Sensory Motor↔ RFRLS-Affectual Reactions↔ RFRLS-Social Relationship↔ RFRLS-Language↑ RFRLS-Sensory Response↔
Fung et al., 2014	OpL	ASD	22.5 (5.8)	12	Pregnenolone 50-250mg/day	N/A	12	ABC-I↑	ABC-L/SW↑ ABC-H/NC↔ ABC-SB↔ ABC-IS↔

									Short Sensory Profile↑ SRS↔ VABS ↔

R = randomized, DB = double-blind, PC = placebo-controlled PDisc = Placebo Discontinuation XO = cross over *single blind for parent training ↑=significant improvement ↔=no change **double blind for responders, open label for placebo non-responders on ATX.

CPRS = Children's Psychiatric Rating Scale, RFRLS = Ritvo-Freeman Real-Life Rating Scale, SIB-Q = Self-Injurious Behavior Questionnaire, SRS = Social Responsiveness Scale, ABC = Aberrant Behavior Checklist, ABC-H/NC = ABC- Hyperactivity/Noncompliance, ABC-I = ABC Irritability, ABC-L/SW = ABC-Lethargy/Social Withdrawal, ABC-IS = ABC-Inappropriate Speech, ABC-SB = ABC-Stereotyped Behavior, CPRS = The Conners' Parent Rating Scale, RSB(-R) = Repetitive Behavior Scale(-Revised), CGI = Clinical Global Impression