

Appendices 1-8

Evidence-Based Recommendations for Monitoring Safety of Second Generation Antipsychotics in Children and Youth

Tamara Pringsheim, Constadina Panagiotopoulos, Jana Davidson, and Josephine Ho for the CAMESA guideline group

Appendix 1 Quality Criteria, USPSTF

Good	<p><i>Studies are graded “good” only if all of the following are met:</i></p> <ul style="list-style-type: none"> Comparable groups assembled Interventions are clearly stated All important outcomes are considered Measurement instruments acceptable and applied equally Outcome assessment is blinded Appropriate attention to confounders in analysis Intention to treat is used Concealment: Adequate measures to conceal allocation to study groups from those responsible for assessing patients for entry in the trial
Fair	<p><i>Studies are graded fair if ANY of the following problems occur, without the fatal flaws listed in the “poor” category:</i></p> <ul style="list-style-type: none"> Generally comparable groups, or some minor problems with follow-up Some but not all important outcomes are considered Some but not all important confounders are accounted for Method of randomization not stated in methods
Poor	<p><i>Studies are graded poor if any of the following fatal flaws exist:</i></p> <ul style="list-style-type: none"> Groups assembled are not comparable Unreliable or invalid measurements are used, or are not applied equally Lack of blinding to outcome assessment Key confounders are not addressed Intention to treat analysis is lacking

Appendix 2 GRADE system criteria for assigning grade of evidence

Type of evidence

Randomized trial = high

Observational study = low

Any other evidence = very low

Decrease grade if:

- Serious (– 1) or very serious (– 2) limitation to study quality
- Important inconsistency (– 1)
- Some (– 1) or major (– 2) uncertainty about directness
- Imprecise or sparse data (– 1)
- High probability of reporting bias (– 1)

Increase grade if:

- Strong evidence of association—significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1)
- Very strong evidence of association—significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2)
- Evidence of a dose response gradient (+1)
- All plausible confounders would have reduced the effect (+1)

Appendix 3 Risperidone Summary Table

Study ID	Diagnosis, number of subjects	Mean dosage	Side effect outcomes reported	Level of evidence	USPSTF Quality Rating	Grade of Evidence	Support
Double-blind, Randomized, Controlled Trials							
Aman 2002	Disruptive behavior and subaverage intelligence, n=118	1.16 mg/day	Mean weight gain Prolactin concentration Extrapyramidal side effects ECG	I	Fair	High	Janssen Research Foundation
Armenteros 2007	ADHD, n=25	1.08 mg/day	Mean weight gain BMI Blood pressure Heart rate Blood cell count Electrolytes Thyroid and kidney function tests	I	Fair	High	Janssen
Buitelaar 2001	Disruptive behavior disorders and subaverage intelligence, n=38	2.9 mg/day	Mean weight gain Prolactin concentration Extrapyramidal side effects QTc interval Liver function Electrolytes Thyroid function Blood pressure Heart rate ECG	I	Fair	High	Janssen-Cilag
Findling 2000	Conduct disorder, n=20	1.03 mg/day (if pt <50kg) or 2.05 mg/day (if pt ≥50kg)	Mean weight gain Neurological side effects (AIMS) Vital signs ECG	I	Good	High	Janssen Research Foundation Stanley Foundation NICHD
Gaffney 2002 Active comparator trial, versus clonidine	Tourette's syndrome, n=21	1.5 mg/day	Weight Blood pressure Pulse ECG Extrapyramidal side effects	I	Fair	High	Tourette's Syndrome Association Janssen Pharmaceutica
Gilbert 2004 Active comparator	Tic disorders, n=19	2.5 mg/day	Mean weight gain Vital signs	I	Fair	High	TEVA Pharmaceuticals NINDS K23

trial, versus pimozide			Extrapyramidal side effects QTc interval				
Haas 2009	Bipolar disorder, n=169	0.5-2.5 mg/day or 3-6 mg/day	Mean weight gain Clinically significant weight gain BMI Prolactin concentration Lipids Glucose Extrapyramidal side effects Vital signs`	I	Fair	High	Johnson & Johnson Pharmaceutical Research & Development
Haas 2009 Active comparator trial, low versus high dose risperidone	Schizophrenia, n=160	1-3 mg/day or 4-6 mg/day	Mean weight gain Prolactin change Extrapyramidal side effects Glucose AIMS, SAS, BARS Vital signs ECG	I	Fair	High	Johnson & Johnson Pharmaceutical Research & Development
Haas 2009	Schizophrenia, n=279	4.00 mg/day (regimen A) or 0.40 mg/day (regimen B)	Mean weight gain Extrapyramidal side effects Prolactin Vital signs ECG	I	Poor	Low	Johnson & Johnson Pharmaceutical Research & Development
Luby 2006	Autistic spectrum disorders, n=23	1.14 mg/day	Mean weight gain Prolactin change Leptin change ECG	I	Poor	Low	Janssen Pharmaceutica
Nagaraj 2006	Autism, n=39	1 mg/day	Mean weight gain Extrapyramidal side effects Pulse Blood pressure	I	Good	High	Postgraduate Institute of Medical Education & Research Sun Pharmaceuticals
Reyes 2006	Disruptive behavior disorders, n=335	0.81 mg/day (if pt <50kg) or 1.22 mg/day (if pt ≥50kg)	Mean weight gain BMI Prolactin concentration Extrapyramidal side effects ECG Vital signs	I	Good	High	Johnson & Johnson Pharmaceutical Research & Development

			Glucose				
RUPP 2002	Autism, n=110	1.8 mg/day	Mean weight gain Extrapyramidal side effects Pulse rate Blood pressure	I	Fair	High	NIMH NIH Korczak Foundation Janssen Pharmaceutica
Shea 2004	Autistic and other pervasive developmental disorders, n=79	1.48 mg/day	Mean weight gain Extrapyramidal side effects Pulse rate Blood pressure	I	Fair	High	Janssen Ortho Inc. Johnson & Johnson Pharmaceutical Research & Development
Sikich 2004 Active comparator trial, versus olanzapine and haloperidol	Psychotic youth, n=50	4.0 mg/day	Mean weight gain BMI Prolactin Lipids Extrapyramidal side effects Glucose	I	Good	High	NIMH UNC Mental Health & Neuroscience NIH Janssen Pharmaceutica Eli Lilly Company Foundation of Hope
Sikich 2008 Active comparator trial versus olanzapine and molindone	Schizophrenia and schizoaffective disorder, n=116	2.8 mg/day	Mean weight gain Extrapyramidal side effects Lipids Glucose Prolactin	I	Good	High	NIMH NIH Eli Lilly Company Janssen Pharmaceutica
Snyder 2002	Conduct/Disruptive behavior disorders and subaverage IQ, n=110	0.98 mg/day	Mean weight gain Prolactin concentration Extrapyramidal side effects QTc interval Heart rate Blood pressure Pulse rate	I	Fair	High	Janssen Research Foundation
Van Bellinghen 2001	Borderline intellectual functioning, n=13	1.2 mg/day	Mean weight gain Clinically significant weight gain Heart rate Blood pressure Extrapyramidal side effects Blood cell count Glucose	I	Fair	High	Janssen Pharmaceutica

Open-label Trials							
Aman 2005	Autism, n=63	Not reported	Mean weight gain BMI Prolactin Blood count Electrolytes ECG Heart rate Blood pressure AIMS	II-1	Poor	Low	NIMH NIH Janssen Pharmaceutica Korczak Foundation
Anderson 2007	Autism, n=63	2.08 mg/day	Mean weight gain Prolactin ECG Vital signs	II-1	Poor	Low	NIMH Korczak Foundation
Biederman 2008	ADHD and bipolar disorder, n=31	1.47 mg/day	Mean weight gain Prolactin concentration Glucose Lipids Blood pressure	II-1	Poor	Low	Janssen Pharmaceutica Stanley Medical Research Institute NIH
Canitano 2006	Autism, n=11	0.6 mg/day	Mean weight gain Extrapyramidal side effects Blood pressure Blood cell counts Liver and renal function tests ECG	II-1	Poor	Low	Not Stated
Capone 2008	Down syndrome, severe intellectual disability, and comorbid autistic spectrum disorders, n=23	0.66 mg/day	Mean weight gain Extrapyramidal side effects	II-1	Poor	Low	Not Stated
Castro-Fornieles 2008	Psychosis, n=110	2.8 mg/day	Weight change BMI change Neurological side effects	II-2	N/A	Low	Carlos III Institute of Health Spanish Department of Health Cooperative Research Thematic Network Spanish Ministry of Health
Correll 2009	Mood spectrum,	Not	Mean weight	II-2	N/A	Low	NIH

	schizophrenia spectrum, and disruptive or aggressive behavior spectrum disorders, n=338	reported	gain BMI Fat mass Waist circumference Lipids Glucose Insulin Blood pressure HDL, LDL				NARSAD Zucker Hillside Hospital Feinstein Institute for Medical Research National Center for Research Resources
Croonenberghs 2005	Disruptive Behavior disorders and subaverage intelligence, n=504	1.6 mg/day	Mean weight gain Extrapyramidal side effects Prolactin concentration Vital signs ECG	II-1	Poor	Low	Johnson & Johnson Pharmaceutical Research & Development
Diler 2002	Autism, n=20	1.53 mg/day	Mean weight gain Extrapyramidal side effects Blood pressure Pulse rate Blood count Liver function tests Thyroid function tests	II-1	Poor	Low	Not Stated
Findling 2004	Disruptive behaviour disorders and subaverage IQ, n=107	1.51 mg/day	Mean weight gain Blood count Electrolytes Liver and kidney function tests Growth hormone Prolactin ECG Extrapyramidal side effects Blood pressure	II-1	Poor	Low	Johnson & Johnson Pharmaceutical Research & Development
Fraguas 2008	Schizophrenia or other psychosis, n=66	3.5 mg/day	Mean weight gain BMI Lipids Glucose Blood pressure HDL, LDL, TSG, FT4, hemoglobin	II-2	N/A	Low	Spanish Ministry of Health Instituto de salud Carlos III REM-TAP Network Fondo de Investigación Sanitaria Asociación

			A1c				Madrilena de Salud Mental NARSAD
Gagliano 2004	Autism, n=20	1.26 mg/day	Mean weight gain Extrapyramidal side effects Prolactin concentration ECG Blood pressure Heart rate	II-1	Poor	Low	Not Stated
Haas 2008	Disruptive behavior disorders, n=232	0.25-0.75 mg/day or 0.5-1.5 mg/day	Mean weight gain Extrapyramidal side effects Glucose Lipids ECG Blood pressure Pulse rate	II-1	Poor	Low	Johnson & Johnson Pharmaceutical Research & Development
Hellings 2001	Mental retardation and autism, n=11	1-3 mg/day	Mean weight gain Blood count	II-1	Poor	Low	NICHD NIMH
Jensen 2008	Schizophrenic spectrum disorders, n=30	3.4 mg/day	Mean weight gain BMI Extrapyramidal side effects Blood pressure Pulse Blood cell count Electrolytes Liver and thyroid function tests	II-1	Poor	Low	AstraZeneca Pharmaceuticals
Kalkan 2010	Mucopolysaccharidosis type III, n=12	0.84 mg/day	Mean weight gain Prolactin concentration Glucose Lipids Extrapyramidal side effects	II-1	Poor	Low	None
Malone 2002	Autism, n=22	1.8 mg/day	Mean weight gain Extrapyramidal side effects Pulse Blood pressure AIMS	II-1	Poor	Low	NIMH

			Blood cell count Liver function tests ECG				
Masi 2001	Pervasive Developmental Disorders, n=24	0.49 mg/day	Mean weight gain Glucose Heart rate Pulse Blood pressure Neurological side effects Liver function tests ECG, EEG	II-1	Poor	Low	Not Stated
Masi 2001 [2]	Pervasive developmental disorders, n=10	0.4 mg/day	Mean weight gain Glucose Extrapyramidal side effects Heart rate Pulse Blood pressure Complete blood cell counts ECG Liver function tests	II-1	Poor	Low	Not Stated
McDougle 1997	Pervasive developmental disorders, n=18	1.8 mg/day	Mean weight gain Extrapyramidal side effects Blood pressure	II-1	Poor	Low	US Public Health Service Yale Children's Clinical Research Center NARSAD Korczak Foundation State of Connecticut NIH
McDougle 2005	Autism, n=63	2.1 mg/day	Not reported	II-1	Poor	Low	NIMH NIH Janssen Pharmaceutica
Miral 2008	Autistic disorder, n=30	2.6 mg/day	Weight Prolactin Hemoglobin Vital signs ECG Extrapyramidal side effects	I	Poor	Low	Janssen-Cilag
Mozes 2006	Schizophrenia, n=25	1.62 mg/day	Mean weight gain	II-1	Poor	Low	None

			Prolactin Extrapyramidal side effects Blood pressure Pulse				
Nicolson 1998	Autism, n=10	1.3 mg/day	Mean weight gain Extrapyramidal side effects Blood pressure Heart rate	II-1	Poor	Low	Janssen Ortho Inc.
Pavuluri 2004	Bipolar disorder, n=37	0.75 mg/day (Li+Risp) and 0.70 mg/day (DVPX+Risp)	Mean weight gain Glucose Prolactin concentration Extrapyramidal side effects Cholesterol Blood pressure Heart rate ECG Electrolytes Blood cell count	II-1	Poor	Low	Not Stated
Pavuluri 2006	Bipolar disorder, n=38	0.99 mg/day	Mean weight gain Extrapyramidal side effects Prolactin P-SEC, AIMS Blood pressure Heart rate Blood cell count ECG	II-1	Poor	Low	Marshall Reynolds Foundation NIH Campus Research Board Janssen Research Foundation
Perry 1997	Pervasive developmental disorder, n=6	2.7 mg/day	Mean weight gain Extrapyramidal side effects Blood cell counts AIMS ECG	II-1	Poor	Low	Not Stated
Ratzoni 2002	N=50	Not reported	Mean weight gain BMI	II-2	N/A	Low	Israeli Ministry of Health
Rausch 2005	Asperger's Disorder, n=13	0.5-1.5 mg/day	Mean weight gain Extrapyramidal side effects AIMS	II-1	Poor	Low	Janssen Pharmaceutica

Reyes 2006 [1]	Disruptive behavior disorders, n=35	1.92 mg/day	Mean weight gain Extrapyramidal side effects BMI Prolactin concentration Glucose Vital signs ECG	II-1	Poor	Low	Not Stated
Reyes 2006 [3]	Disruptive behavior disorder, n=48	1.83 mg/day	Mean weight gain Extrapyramidal side effects Glucose Prolactin concentration Vital signs ECG Glucose	II-1	Poor	Low	Johnson & Johnson Pharmaceutical Research & Development
Thomsen 2004	Obsessive-compulsive disorder, n=17	1-2 mg/day	Mean weight gain BMI	II-1	Poor	Low	Not Stated
Turgay 2002	Disruptive behavior disorders and subaverage IQ, n=77	1.38 mg/day	Mean weight gain Prolactin concentration Extrapyramidal side effects Glucose Pulse Blood pressure Blood count Liver function tests Electrolytes Heart rate ECG	II-1	Poor	Low	Janssen Research Foundation
Vercellino 2001	Autism, n=9	0.5-3 mg/day	Extrapyramidal side effects Glucose Blood count Liver function EEG	II-2	N/A	Low	Not Stated
Zuddas 2000	Pervasive developmental disorder, n=11	2.7 mg/day	Mean weight gain Extrapyramidal side effects Neurological examinations Vital signs EEG Blood cell count	II-1	Poor	Low	Not Stated
Case Series,							

Case Reports, and Retrospective Studies							
Calarge 2009	Any psychiatric disorder, n=99	0.02 to 0.04 mg per kg per day	Weight Height BMI Percent body fat Waist circumference Blood pressure Glucose Insulin Total cholesterol, HDL, LDL Triglycerides TSH	III	N/A	Very Low	NIH
Koller 2003	Not specified, n=31, 3 pediatric cases	Not specified	Diagnosis of pancreatitis	III	N/A	Very Low	Not Stated
Koller 2003	Not specified, n=131, 12 pediatric cases	Not specified	Diagnosis of hyperglycemia or diabetes mellitus	III	N/A	Very Low	Not Stated

Appendix 4 Olanzapine Summary Table

Study ID	Diagnosis, number of subjects	Mean dosage	Side effect outcomes reported	Level of evidence	USPSTF Quality Rating	Grade of Evidence	Support
Double-blind, Randomized, Controlled Trials							
Hollander 2006	Pervasive Developmental Disorder, n=11	10 mg/day	Mean weight gain Extrapyramidal side effects Blood pressure	I	Fair	High	Lilly Research Laboratories
Kryzhanovskaya 2009	Schizophrenia, n=107	11.1 mg/day	Mean weight gain BMI Lipids Prolactin Extrapyramidal side effects Glucose Blood pressure ECG Electrolytes	I	Fair	High	Eli Lilly Company
Kumra 2008 Active comparator trial, versus clozapine	Schizophrenia, n=39	26.2 mg/day	Mean weight gain BMI Lipids Glucose Extrapyramidal side effects	I	Good	High	Not Stated
Shaw 2006 Active comparator trial, versus clozapine	Schizophrenia, n=25	18 mg/day	Mean weight gain BMI Lipids Extrapyramidal side effects Blood pressure	I	Good	High	Not Stated
Sikich 2004 Active comparator trial, versus risperidone and haloperidol	Psychotic youth, n=50	12.3 mg/day	Mean weight gain BMI Prolactin Lipids Extrapyramidal side effects Glucose	I	Good	High	NIMH UNC Mental Health & Neuroscience NIH Janssen Pharmaceutica Eli Lilly Company Foundation of Hope
Sikich 2008 Active comparator trial, versus risperidone and molindone	Schizophrenia and schizoaffective disorder, n=116	11.4 mg/day	Mean weight gain Extrapyramidal side effects Lipids Glucose	I	Good	High	NIMH NIH Eli Lilly Company Janssen Pharmaceutica

			Prolactin				
Tohen 2007	Bipolar disorder, n=161	8.9 mg/day	Mean weight gain BMI Glucose Lipids Prolactin Extrapyramidal side effects Blood pressure ECG	I	Fair	High	Eli Lilly Company
Open-label trials							
Arango 2009	Psychosis, n=50	9.7 mg/day	Mean weight gain BMI Blood pressure Heart rate QTc Glucose Lipids Blood cell counts Electrolytes Renal and liver function Hemoglobin A1c	II-1	Poor	Low	AstraZeneca Pharmaceuticals Fundacion Alicia Koplowitz instituto de Salud Carlos III
Castro-Fornieles 2008	Psychosis, n=110	11.7 mg/day	Weight change BMI change Neurological side effects	II-2	N/A	Low	Carlos III Institute of Health Spanish Department of Health Cooperative Research Thematic Network Spanish Ministry of Health
Correll 2009	Mood spectrum, schizophrenia spectrum, and disruptive or aggressive behavior spectrum disorders, n=338	Not reported	Mean weight gain BMI Fat mass Waist circumference Lipids Glucose Insulin Blood pressure HDL, LDL	II-2	N/A	Low	NIH NARSAD Zucker Hillside Hospital Feinstein Institute for Medical Research National Center for Research Resources
Crocq 2007	Schizophreniform disorder, n=52	16.6 mg/day	Mean weight gain	II-2	N/A	Low	Not Stated

			BMI				
Dittmann 2008	Schizophrenic disorders, n=96	18.3 mg/day	Mean weight gain Extrapyramidal side effects Prolactin Lipids Glucose Blood pressure	II-1	Poor	Low	Lilly Deutschland GmbH
Fido 2008	Autism, n=40	7.5 mg/day	Mean weight gain Extrapyramidal symptoms Glucose Lipids ECG	II-1	Poor	Low	Not Stated
Fleischhaker 2008	N=61	10.2 mg/day	Mean weight gain BMI	II-2	N/A	Low	Janssen-Cilag
Fraguas 2008	Schizophrenia or other psychosis, n=66	9.8 mg/day	Mean weight gain BMI Lipids Glucose Blood pressure HDL, LDL, TSG, FT4, hemoglobin A1c	II-2	N/A	Low	Spanish Ministry of Health Instituto de salud Carlos III REM-TAP Network Fondo de Investigation Sanitaria Asociation Madrilenia de Salud Mental NARSAD
Jensen 2008	Schizophrenic spectrum disorders, n=30	14.0 mg/day	Mean weight gain BMI Extrapyramidal side effects Blood pressure Pulse Blood cell count Electrolytes Liver and thyroid function tests	II-1	Poor	Low	AstraZeneca Pharmaceuticals
Milin 2006	Asperger Disorder, n=12	8.25 mg/day	Mean weight gain BMI Glucose ECG AIMS	II-1	Poor	Low	Eli Lilly Canada
Mozes 2003	Schizophrenia, n=9	15.56 mg/day	Mean weight gain Extrapyramidal	II-1	Poor	Low	Not Stated

			side effects Blood pressure Complete blood count Liver function tests ECG, EEG				
Mozes 2006	Schizophrenia, n=25	8.18 mg/day	Mean weight gain Prolactin Extrapyramidal side effects Blood pressure Pulse	II-1	Poor	Low	Not Stated
Ratzoni 2002	n=50	Not reported	Mean weight gain BMI	II-2	N/A	Low	Israeli Ministry of Health
Ross 2003	Schizophrenia, n=20	10.4 mg/day	Mean weight gain BMI Glucose Extrapyramidal side effects Blood pressure	II-1	Poor	Low	Veterans' Administration Research Services Public Health Service Eli Lilly Company
Case Series, Case Reports, and Retrospective Studies							
Koller 2003	Not specified, 69 cases associated with olanzapine, 4 cases in children	Not reported	Reported diagnosis of pancreatitis	III	N/A	Very Low	Not Stated
Staller 2006	Not specified, n=50, 7 taking olanzapine	10 mg/day	Prolactin	III	N/A	Very Low	AstraZeneca Pharmaceuticals
Domon 2001	Mood disorder, case report	20 mg	Weight BMI Glucose Triglycerides Cholesterol	III	N/A	Very Low	Not Stated
Courvoisie 2004	Bipolar disorder, case report	2.5 mg	Weight BMI Glucose	III	N/A	Very Low	Not Stated

Appendix 5 Quetiapine Summary Table

Study ID	Diagnosis, number of subjects	Mean dosage	Side effects outcomes reported	Level of evidence	USPSTF quality rating	Grade of Evidence	Support
Double-blind, Randomized, Controlled Trials							
Connor 2008	Conduct disorder n=19	294 mg	Mean weight change BMI Blood pressure, heart rate QTc interval Prolactin change Barnes Akathisia Scale Abnormal Involuntary Movement Scale	I	Fair	High	AstraZeneca Pharmaceuticals
DelBello 2006 Active comparator trial versus divalproex	Bipolar disorder, mania n=50	412 mg	Simpson Angus Rating Scale Barnes Akathisia Scale Abnormal Involuntary Movement Scale QTc interval Liver function tests Mean weight gain Blood pressure, heart rate	I	Good	High	AstraZeneca Pharmaceuticals
DelBello 2002	Bipolar disorder, mania n=30	432 mg	Change in QTc interval Change in prolactin Change in TSH Mean weight gain Blood pressure, heart rate Simpson Angus Rating Scale Barnes Akathisia Scale Abnormal Involuntary Movement Scale	I	Fair	High	AstraZeneca Pharmaceuticals
DelBello 2009	Depressed adolescents with bipolar disorder n=32	403 mg	QTc interval change Change in triglycerides, total cholesterol, LDL, HDL or glucose Incidence of high glucose, high cholesterol, high LDL, low HDL or high triglycerides	I	Good	High	AstraZeneca Pharmaceuticals

			Weight gain Blood pressure, heart rate Change in BMI Change in prolactin Simpson Angus Rating Scale Barnes Akathisia Scale Abnormal Involuntary Movement Scale				
Open-label Trials							
Arango 2009	Psychosis n=50	533 mg	Weight gain BMI Barnes Akathisia Scale Simpson Angus Rating Scale Liver function tests Fasting glucose, lipid profile Hemoglobin A1c Prolactin ECG Blood pressure, heart rate	II-1	Poor	Low	AstraZeneca Pharmaceuticals Fundacion Alicia Koplowitz Instituto de Salud Carlos III
Castro- Fornieles 2008	Psychosis n=110	627 mg	Weight change BMI change Neurological side effects	II-2	n/a	Low	Carlos III Institute of Health Spanish Department of Health Cooperative Research Thematic Network Spanish Ministry of Health
Corell 2009	Psychotic, mood or aggressive spectrum disorders n=338; 45 treated with olanzapine in analysis		Mean weight gain Weight change as percentage of baseline Fat mass BMI, BMI change as percentage of baseline, BMI z score, BMI percentile Waist circumference Change in glucose Change in insulin Change in HOMA-IR Ratio of	II-2	n/a	Low	National Institutes of health NARSAD Zucker Hillside Hospital Feinstein Institute for Medical Research National Center for Research Resources

			triglycerides to HDL Change in total cholesterol Change in LDL Change in HDL Change in triglycerides Change in non-HDL cholesterol				
Delbello 2007	Adolescents with mood symptoms	460 mg	Mean weight change Mean BMI change Heart rate Blood pressure QTc interval Simpson Angus Rating Scale Barnes Akathisia Scale Abnormal Involuntary Movement Scale Liver function tests Prolactin Thyroid stimulating hormone	II-1	Poor	Low	Stanely Medical Research Institute Chevy Chase MD. AstraZeneca Pharmaceuticals
Duffy 2009	Bipolar disorder n=21	341 mg	Mean weight gain BMI Rate of clinically significant weight gain (>7% baseline) Thyroid function Prolactin Liver function tests Cholesterol, LDL, HDL, triglycerides ECG	II-1	Poor	Low	AstraZeneca Pharmaceuticals
Findling 2007	Conduct disorder n=9	150 mg	Barnes Akathisia Scale Abnormal Involuntary Movement Scale Mean weight gain Heart rate, blood pressure Prolactin, thyroid profile Fasting morning metabolic profile (components not listed)	II-1	Poor	Low	AstraZeneca Pharmaceuticals NIH
Fraguas 2008	Mixed sample; any psychiatric disorder requiring	391 mg	Mean weight change BMI BMI z score	II-2	n/a	Low	Spanish Ministry of Health Instituto de salud Carlos III

	antipsychotic treatment n= 66		Fasting glucose, triglycerides, total cholesterol, HDL, LDL, TSH, free thyroxin, haemoglobin Alc Blood pressure				REM-TAP Network Fondo de Investigation Sanitaria Asociation Madrilenas de Salud Mental NARSAD
Jensen 2008	Schizophrenia spectrum disorders n=30	611 mg	Mean weight gain BMI Blood pressure, heart rate Abnormal Involuntary Movement Scale Simpson Angus Rating Scale Liver function tests Thyroid function tests ECG	II-1	Poor	Low	AstraZeneca Pharmaceuticals
Martin 1999	Autistic Disorder n=6	225 mg	Weight change Blood pressure, heart rate Abnormal Involuntary Movement Scale	II-1	Poor	Low	Not Stated
Schimmelmann 2007	Schizophrenia Spectrum Disorders n=56	584 mg	Simpson Angus Rating Scale Barnes Akathisia Scale Mean weight change Mean BMI change Rate of greater than 7% weight gain Serum thyroxine and thyroid stimulating hormone Prolactin Total cholesterol Blood pressure	II-1	Poor	Low	AstraZeneca Pharmaceuticals
Case Series, Case Reports, and Retrospective Studies							
Koller 2004	Not specified, 46 reports identified	423 mg	Newly diagnosed diabetes on the basis of fasting glucose level of 126 mg/dl or greater, a random glucose level of 200 mg/dl or greater, or elevated glycohemoglobin	III	Poor	Very Low	Not Stated

			values				
Staller, 2006	Pediatric psychiatry outpatients	200 mg	Prolactin levels	III	Poor	Very Low	AstraZeneca Pharmaceuticals

Appendix 6 Aripiprazole Summary Table

Study ID	Diagnosis, number of subjects	Mean dosage	Side effect outcomes reported	Level of evidence	USPSTF Quality Rating	Grade of Evidence	Support
Double-blind, Randomized, Controlled Trials							
Findling 2008	Schizophrenia n=302	10 mg or 30 mg	Incidence of extrapyramidal symptoms Barnes Akathisia Rating Scale AIMS score Mean weight change Mean BMI change Fasting glucose change Incidence of high glucose Change in total cholesterol Change in triglycerides Change in HDL Change in prolactin Mean change in QTc interval	I	Fair	High	Ostuka Pharmaceutical Co.
Findling 2009	Bipolar disorder, manic or mixed episode n=296	10 mg or 30 mg	Incidence of extrapyramidal symptoms Mean BMI change Rate of clinically significant weight gain (>7%) Mean weight gain Incidence of high glucose Incidence of high total cholesterol Incidence of high triglycerides Incidence of low HDL Mean change in prolactin Incidence of abnormal QTc intervals Blood pressure Heart rate	I	Fair	High	Ostuka Pharmaceutical Co. Ogilvy Healthworld Medical Education
Marcus 2009	Autistic Disorder n=218	10.0 mg	Mean weight change Rate of clinically significant weight gain (>7% baseline) BMI change from baseline	I	Fair	High	Bristol-Myers Squibb Ostuka Pharmaceutical Co Ogilvy

			<p>Incidence of extrapyramidal side effects</p> <p>Change in Abnormal Involuntary Movement Scale (AIMS) score from baseline</p> <p>Change in prolactin</p> <p>Incidence of high triglycerides</p> <p>Incidence of high LDL or high total cholesterol</p> <p>Incidence of low HDL</p> <p>Incidence of high glucose</p> <p>Change in QTc interval</p>				Healthworld Medical Education
Owen 2009	Autistic Disorder n=97	7.42 mg	<p>Mean weight change</p> <p>Rate of clinically significant weight gain (>7% baseline)</p> <p>Incidence of high triglycerides</p> <p>Incidence of high LDL</p> <p>Incidence of low HDL</p> <p>Incidence of high glucose</p> <p>Incidence of prolonged QTc</p> <p>Prolactin change from baseline</p> <p>Incidence of any extrapyramidal event</p>	I	Good	High	Bristol-Myers Squibb Ostuka Pharmaceutical Co Ogilvy Healthworld Medical Education
Tramontina 2009	Bipolar disorder comorbid with ADHD n=43	13.6 mg	<p>Mean weight change</p> <p>Incidence of extrapyramidal symptoms</p>	I	Good	High	Conselho Nacional de Desenvolvimento Cientifico e Tecnologico Hospital de Clinicas de Porto Alegre Bristol-Myers Squibb
Open-label trials							
Stigler 2009	PDD NOS Asperger's Disorder n= 25	7.8 mg	<p>Heart rate</p> <p>Blood pressure</p> <p>Change in QTc interval</p> <p>Prolactin level</p> <p>Mean weight gain</p> <p>BMI</p> <p>Incidence of high glucose</p>	II-1	Poor	Low	American Academy of Child & Adolescent Psychiatry Daniel X & Freedman Bristol-Myers Squibb NIH

			Incidence of high triglycerides Incidence of high cholesterol Incidence of high LDL Simpson Angus Rating scale AIMS score				NIMH
Seo 2008	Tourette or Chronic tic disorder n=15	8.2 mg	Mean BMI	II-1	Poor	Low	Not Stated
Corell 2009	Psychotic, mood or aggressive spectrum disorders n=338; 41 treated with aripiprazole included in analysis	Not given	Mean weight gain Weight change as percentage of baseline Fat mass BMI, BMI change as percentage of baseline, BMI z score, BMI percentile Waist circumference Change in glucose Change in insulin Change in HOMA-IR Ratio of triglycerides to HDL Change in total cholesterol Change in LDL Change in HDL Change in triglycerides Change in non-HDL cholesterol	II-2	n/a	Low	National Institutes of health NARSAD Zucker Hillside Hospital Feinstein Institute for Medical Research National Center for Research Resources
Findling 2009	Autistic Disorder n=330	Not given	Mean change from baseline in body weight z-score BMI percentiles Incidence of high glucose Incidence of high cholesterol Incidence of high LDL Incidence of low HDL Incidence of high triglycerides Incidence of extrapyramidal side effects	II-1	Poor	Low	Not Stated

Appendix 7 Clozapine Summary Table

Study ID	Diagnosis, number of subjects	Mean dosage	Side effect outcomes reported	Level of evidence	USPSTF Quality Rating	Grade of Evidence	Support
Double-blind, Randomized, Controlled Trials							
Kumra 1996 Active comparator trial, versus haloperidol	Schizophrenia, n=21	176 mg/day	Mean weight gain Extrapyramidal side effects ECG Blood counts Thyroid functions Liver chemistries Prolactin	I	Good	High	Sandoz Pharmaceuticals NIH
Kumra 2008 Active comparator trial, versus olanzapine	Schizophrenia, n=39	403.1 mg/day	Mean weight gain BMI Lipids Glucose Extrapyramidal side effects	I	Good	High	Not Stated
Shaw 2006 Active comparator trial, versus olanzapine	Schizophrenia, n=25	327 mg/day	Mean weight gain BMI Lipids Extrapyramidal side effects Liver function tests Electrolytes	I	Good	High	Not Stated
Open-label Trials							
Kumra 2008 [2]	Schizophrenia, n=33	Not reported	Mean weight gain BMI Glucose Lipids Prolactin	II-1	Poor	Low	NIMH
Turetz 1997	Schizophrenia, n=11	227.3 mg/day	Extrapyramidal side effects Full blood cell count ECG	II-1	Poor	Low	Emounth Foundation
Fleischhaker 2008	N=61	312 mg/day	Mean weight gain BMI	II-2	N/A	Low	Janssen-Cilag
Case Series, Case Reports, and Retrospective Studies							
Gogtay 2002	Schizophrenia, n=2	Not reported	Extrapyramidal side effects	III	N/A	Very Low	Not Stated
Koller 2003	Not specified, 82 cases of pancreatitis associated with clozapine use	306.7 mg/day	Reported cases of pancreatitis	III	N/A	Very Low	Not Stated

Appendix 8 Ziprasidone Summary Table

Study ID	Diagnosis, number of subjects	Mean dosage	Side effect outcomes reported	Level of evidence	USPSTF Quality Rating	Grade of Evidence	Support
Double-blind, Randomized, Controlled Trials							
Sallee 2000	Tourette's syndrome, n=28	28.2 mg/day	Mean weight gain Prolactin Blood pressure Pulse rate ECG	I	Fair	High	Pfizer Central Research
Open-label trials							
Blair 2005	Tourette's syndrome, OCD, or PDD, n=20	30 mg/day	Heart rate Pulse rate QTc intervals	II-1	Poor	Low	Korzack Foundation Scientist Career Development Public Health Service NIMH
DeIbello 2008	Bipolar mania, schizophrenia, or schizoaffective disorder, n=63	Not reported	Mean weight gain Lipids Extrapyramidal side effects Prolactin Blood pressure Pulse rate QTc interval	II-1	Poor	Low	Pfizer Inc.
Malone 2007	Autism, n=12	98.3 mg/day	Height Weight Blood pressure Pulse CBC Liver functions Serum glucose Lipid profile Prolactin ECG AIMS Simpson Angus Scale	II-1	Poor	Low	Pfizer Inc.
Biederman 2007	Bipolar disorder, n=21	57.3 mg/day	Weight BMI BMI z score Lipid profile Prolactin Glucose Blood pressure Pulse ECG	II-1	Poor	Low	Pfizer Inc.
Case Series, Case Reports, and Retrospective Studies							
McDougle 2002	Autism, n=12	59.23 mg/day	Weight Neurological side effects	III	Poor	Very Low	NARSAD Daniel X. & Freedman

							Department of Housing & Urban Development NIMH
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