Summary of Risk Management Plan for Aripiprazole

This is a summary of the risk management plan (RMP) for aripiprazole. The RMP details important risks of aripiprazole, how these risks can be minimised, and how more information will be obtained about aripiprazole's risks and uncertainties (missing information).

Aripiprazole's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how aripiprazole should be used.

This summary of the RMP for aripiprazole should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of aripiprazole's RMP.

I: The Medicine and What it is Used for

Aripiprazole (Abilify) is authorised for schizophrenia in adults and in adolescents aged 15 years and older, moderate to severe manic episodes in Bipolar I Disorder and the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment, treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older and for rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate (see SmPC for the full indication). It contains aripiprazole as the active substance and it is given orally or intramuscularly. Forms and strengths are as follows:

- Abilify tablets: 1 mg, 2 mg, 3 mg, 5 mg, 6 mg, 10 mg, 12 mg, 15 mg, 20 mg and 30 mg
- Abilify orally disintegrating tablets: 3 mg, 5 mg, 6 mg, 10 mg, 12 mg, 15 mg, 20 mg, 24 mg and 30 mg
- Abilify oral solution: 1 mg/mL
- Abilify powder: 10 mg aripiprazole/1 g powder
- Abilify solution for injection (immediate release) for IM use: 7.5 mg/mL

Aripiprazole (Abilify Maintena) is authorised for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole (see SmPC for the full indication). It contains aripiprazole as the active substance and it is given intramuscularly in 300 mg/vial or pre-filled dual chamber syringe and 400 mg/vial or pre-filled dual chamber syringe.

Further information about the evaluation of aripiprazoles's benefits can be found in aripiprazole's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002755/human_med_001711.jsp&mid=WC0b01ac058001d124

II: Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of aripiprazole, together with measures to minimise such risks and the proposed studies for learning more about aripiprazole's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

II.A: A List of Important Risks and Missing Information

Important risks of aripiprazole are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of aripiprazole. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 6.1.2.1-1 II.A-1: List of Important Risks and Missing Information- Abilify	
Important Identified Risks	• EPS, including tardive dyskinesia
Important Potential Risks	• Orthostatic hypotension
Missing Information	• Use in Pregnancy and Lactation

Table 6.1.2.1-2 II.A-2: List of Important Risks and Missing Information- Abilify Maintena	
Important Identified Risks	• EPS, including tardive dyskinesia •
Important Potential Risks	• Orthostatic hypotension
Missing Information	• Use in Pregnancy and Lactation • Use in Elderly Patients above 65 Years of Age

II.B: Summary of Important Risks

Table 6.1.2.2-1 II.B-1: Important Identified Risk: EPS, including tardive dyskinesia	
Evidence for linking the risk to the medicine	
Risk factors and risk groups	<u>EPS Risk Factors:</u> Age, gender, diagnosis of mood disorder, cognitive difficulties, alcohol and substance abuse, exposure to antipsychotic treatments (type and dose), use of concomitant medications, and diabetes.[343] <u>Tardive Dyskinesia Risk Factors:</u>

Table 6.1.2.2-1 II.B-1: Important Identified Risk: EPS, including tardive dyskinesia	
	Presence or history of EPS, advanced age, diagnosis of mood disorders or cognitive difficulties, alcohol and substance abuse, antipsychotic treatment (type and dose), use of concomitant medications, and diabetes.[290,297,298]
Risk minimisation measures	**Routine risk minimisation measures:** - Warnings & Precautions, section 4.4 of SmPC - Undesirable effects, section 4.8 of the SmPC **Additional risk minimisation measures: None**
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS Study No. 15893N- Extrpyramidal symptoms in patients being treated with Abilify Maintena® Cohort Study with a 2-year follow-up using European automated healthcare databases See section II.C of this summary for an overview of the post-authorisation development plan.

Table 6.1.2.2-2 II.B-2: Important Potential Risk: Orthostatic Hypotension	
Evidence for linking the risk to the medicine	SCS - Bipolar[178]; SCS - Low-dose[252]; SCS - Adjunctive MDD[253]; SCS - Solution for Injection[254]; SCS - Bipolar Pediatrics[253] CSR - 31-03-240[255]; CSR - 31-03-241[256]; SCS - Adjunctive Bipolar[257]; SCS - Autism[258]; CSR – 31-09-266[259]; CSR – 31-09-267[260]; CSR – 31-12-293[261]; CSR 31-12-294[262]; CSR – 31-97-303[263] <u>Aripiprazole IM Depot studies in adult schizophrenia</u>: CN138-020[264]; 031-07-002[301]; 31-05-244[266]; 31-11-289[267]; 31-07-246[268]; 31-07-247{CSR_247}; 31-08-248[270]; 031-08-003[265]; 031-10-002[271]; 31-11-283[272]; 31-11-284[302]; 31-10-270[273]; 31-11-290[274]; 31-12-298[275]; 31-12-291[276]; 31-12-297[277].

Table 6.1.2.2-2 II.B-2: Important Potential Risk: Orthostatic Hypotension	
Risk factors and risk groups	• Advanced age • Use of psychotropic medications (e.g., dopaminergic drugs, antidepressants, neuroleptic agents)[251] • Use of antianginal drugs or antihypertensive and vasodilator therapy[249] • Medical conditions, including hypovolemia, defects of vasomotor reflexes, and autonomic nervous system dysfunction (as may occur in diabetes and Parkinsonism). Drug-induced orthostatic hypotension remains a concern[247,251] • Prolonged and severe orthostatic hypotension has been associated with stroke and myocardial infarction[304] • Drug-induced orthostatic hypotension and elderly patients: – Orthostatic hypotension is associated with significant morbidity and mortality, especially elderly patients in acute-care settings[249] ranging from mild symptoms (dizziness) to severe symptoms, such as syncope (leading to fractures or other injuries and immobility)[304] – Approximately one third of all falls in nursing homes are attributed to psychotropic drug use.[305]
Risk minimisation measures	**Routine risk minimisation measures:** - Warnings & Precautions, section 4.4 of SmPC - Undesirable effects, section 4.8 of the SmPC **Additional risk minimisation measures: None**

Table 6.1.2.2-3 II.B-3: Missing Information: Use in Pregnancy and Lactation	
Risk minimisation measures	**Routine risk minimisation measures:** - Pregnancy and lactation, section 4.6 of the SmPC **Additional risk minimisation measures: None**

Table 6.1.2.2-4	II.B-4 Missing Information: Use in Elderly Patients above 65 Years of Age
Risk minimisation measures	**Routine risk minimisation measures:** - Posology and method of administration, section 4.2 of the SmPC -Warnings & Precautions, section 4.4 of SmPC **Additional risk minimisation measures: None**

II.C: Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of aripiprazole.

II.C.2 Other Studies in Post-authorisation Development Plan

PASS Study No. 15893N- Extrpyramidal symptoms in patients being treated with Abilify Maintena® Cohort Study with a 2-year follow-up using European automated healthcare databases.

Purpose of the study: further assess the risk of EPS-related events linked to the use of Abilify Maintena in clinical practice

Table 6.1.2.3-1 List of Studies in Post-Authorization Development Plan				
Study / activity (including study number)	**Objectives**	**Safety concerns / efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
Study No. 15893N-Extrpyramidal symptoms in patients being treated with Abilify Maintena® Cohort Study with a 2-year follow-up using European automated healthcare databases	Further characterize the risk of EPS-related events of aripiprazole IM depot	Further assess the risk of EPS-related events linked to the use of Abilify Maintena in clinical practice	Ongoing	31-Mar-2021

References

1 Bebbington P and Ramana R. The epidemiology of bipolar affective disorder. Soc Psychiatr Epidemiol 1995;30:279-292.

2 Rasanen P, Tiihonen J, Hakko H. The incidence and onset-age of hospitalized bipolar affective disorder in Finland. J Affect Disord 1998;48:63-68.

3 Kennedy N, Everitt B, Boydell J, van Os J, Jones PB, Murray RM. Incidence and distribution of first-episode mania by age: Results from a 35-year study. Psychological Medicine 2005;35:855-863.

4 Waraich P, Goldner EM, Somers JM, Hsu L. Prevalence and incidence studies of mood disorder: A systematic review of the literature. Can J Psychiatry 2004;49:124-138.

5 Pini S, de Queiroz V, Pagnin D, et al. Prevalence and burden of bipolar disorder in European countries. Eur Neuropsychopharmacol 2005;15:425-434.

6 de Zelicourt M, Dardennes R, Verdoux H, et al. Frequency of hospitalizations and inpatient care costs of manic episodes. Pharmacoeconomics 2003;21:1081-1090.

7 Bijl RV, Ravelli A, van Zessen G. Prevalence of psychiatric disorder in the general population: Results of the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 1998;33:587-595.

8 Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorder in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19.

9 Angst J and Preisig M. Course of a clinical cohort of unipolar, bipolar and schizoaffective patients: Results of a prospective study from 1959 to 1985. Schweiz Arch Neurol Psychiatr 1995;146:5-16.

10 Soldani F, Sullivan PF, Pedersen NL. Mania in the Swedish Twin Registry: Criterion validity and prevalence. Austral NZ J Psychiatry 2005;39:235-243.

11 Judd LL and Akiskal HS. The prevalence and disability of bipolar spectrum disorders in the US population: Re-analysis of the ECA database taking into account subthreshold cases. J Affect Disord 2003;73:123-131

12 Dean K, Walsh E, Morgan C, et al. Aggressive behaviour at first contact with services: Findings from the AESOP First Episode Psychosis study. Psychol Med 2007;37:547-557.

13 Harrington R and Myatt T. Is preadolescent mania the same condition as adult mania? A British perspective. Biol Psychiatry 2003;53(11):961-969.

14 Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: A review of the past 10 years. J Am Acad Child Adolesc Psychiatry 2005;44(9): 846-871.

15 Kessler RC, Avenevoli S, Ries Merikangas K. Mood disorders in children and adolescents: An epidemiologic perspective. Biol Psychiatry 2001;49(12):1002-1014.

16 Carlson GA and Meyer SE. Bipolar disorder in youth. Curr Psychiatry Rep 2000; 2(2): 90-94.

17 Duffy A. Does bipolar disorder exist in children? A selected review. Can J Psychiatry 2007;52:409-417.

18 Geller B, Tillman R, Bolhofner K, Zimerman B. Child bipolar I disorder: Prospective continuity with adult bipolar I disorder; characteristics of second and third episodes; predictors of 8-year outcome. Arch Gen Psychiatry 2008;65:1125-1133.

19 Dilsaver SC and Akiskal HS. Preschool-onset mania: incidence, phenomenology and family history. J Affect Disord 2004; 82S:S35-S43

20 Luby JL, Tandon M, Belden A. Preschool bipolar disorder. Child Adolesc Psychiatr Clin N Am 2009;18:391-403.

21 Geller B, Zimerman B, Williams M et al. DSM-IV mania symptoms in a prepubertal and early adolescent bipolar disorder phenotype compared to attention-deficit hyperactive and normal controls. J Child Adolesc Psychopharmacol 2002;12:11-25.

22 Demeter CA, Townsend LD, Wilson M, Findling RL. Current research in child and adolescent bipolar disorder. Dialogues Clin Neurosci 2008;10:215-228.

23 Carlson GA and Kashani JH. Manic symptoms in a non-referred adolescent population. J Affect Disord 1988;15:219-226.

24 Lewinsohn PM, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: Prevalence, phenomenology, comorbidity, and course. J Am Acad Child Adolesc Psychiatry 1995;34:454-463.

[25] Birmaher B, Axelson D, Monk K, et al. Lifetime psychiatric disorders in school-aged offspring of parents with bipolar disorder: The Pittsburgh Bipolar Offspring study. Arch Gen Psychiatry 2009;66:287-29

[26] Geller B, Tillman R, Craney JL, Bolhofner K. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch Gen Psychiatry 2004;61:459-467.

[27] Biederman J, Faraone SV, Wozniak J, et al. Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. J Psychiatr Res 2005;39:611-622.

[28] Soutullo CA, Chang KD, Diez-Suarez A, et al. Bipolar disorder in children and adolescents: International perspective on epidemiology and phenomenology. Bipolar Disorders 2005;7:497-506.

[29] Dubicka B, Carlson GA, Vail A, Harrington R. Prepubertal mania: Diagnostic differences between US and UK clinicians. Eur Child Adolesc Psychiatry 2008;17:153-16.

[30] Costello EJ, Angold A, Burns BJ, et al. The Great Smoky Mountains Study of Youth. Goals, design, methods, and the prevalence of DSM-III-R disorders. Arch Gen Psychiatry 1996;53:1129-113.

[31] Johnson JG, Cohen P, Brook JS. Associations between bipolar disorder and other psychiatric disorders during adolescence and early adulthood: A community-based longitudinal investigation. Am J Psychiatry 2000;157:1679-1681.

[32] Verhulst FC, van der Ende J, Ferdinand RF, Kasius MC. The prevalence of DSM-III-R diagnoses in a national sample of Dutch adolescents. Arch Gen Psychiatry 1997;54:329-336.

[33] Meltzer H, Gatward R, Goodman R, Ford T. The mental health of children and adolescents in Great Britain. Summary report. 2000;1-24.

[34] Ford T, Goodman R, Meltzer H. The British Child and Adolescent Mental Health Survey 1999: The prevalence of DSM-IV disorders. J Am Acad Child Adolesc Psychiatry 2003;42:1203-1211.

[35] Youngstrom E, Youngstrom JK, Starr M. Bipolar diagnoses in community mental health: Achenbach Child Behavior Checklist profiles and patterns of comorbidity. Biol Psychiatry 2005;58:569-575.

[36] Sourander A. Combined psychopharmacological treatment among child and adolescent inpatients in Finland. Eur Child Adolesc Psychiatry 2004;13:179-184.

[37] Thomsen PH, Moller LL, Dehlholm B, Brask BH. Manic-depressive psychosis in children younger than 15 years: A register-based investigation of 39 cases in Denmark. Acta Psychiatr Scand 1992;85:401-406.

[38] Tramontina S, Schmitz M, Polanczyk G, Rohde LA. Juvenile bipolar disorder in Brazil: Clinical and treatment findings. Biol Psychiatry 2003;53:1043-1049.

[39] Reddy YCJ, Girimaji S, Srinath S. Clinical profile of mania in children and adolescents from the Indian subcontinent. Can J Psychiatry 1997;42:841-846.

[40] Alexander PJ and Raghavan R. Childhood mania in India. J Am Acad Child Adolesc Psychiatry 1997;36:1650-165

[41] Chilakamarri JK, Filkowski MM, Ghaemi SN. Misdiagnosis of bipolar disorder in children and adolescents: A comparison with ADHD and major depressive disorder. Ann Clin Psychiatry 2011;23:25-29.

[42] Leibenluft E and Rich BA. Pediatric bipolar disorder. Annu Rev Clin Psychol 2008;4:163-187.

[43] Harpaz-Rotem I, Leslie DL, Martin A, Rosenheck RA. Changes in child and adolescent inpatient psychiatric admission diagnoses between 1995 and 2000. Soc Psychiatry Psychiatr Epidemiol 2005;40:642-647.

[44] Case BG, Olfson M, Marcus SC, Siegel C. Trends in the inpatient mental health treatment of children and adolescents in US community hospitals between 1990 and 2000. Arch Gen Psychiatry 2007;64:89-96.

[45] Blader JC and Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. Biol Psychiatry 2007;62:107-114.

[46] Moreno C, Laje G, Blanco C, et al. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. Arch Gen Psychiatry 2007;64:1032-1039.

[47] Harpaz-Rotem I and Rosenheck RA. Changes in outpatient psychiatric diagnosis in privately insured children and adolescents from 1995 to 2000. Child Psychiatry Hum Dev 2004;34:329-340.

[48] Perlis RH, Miyahara S, Marangell LB, et al. Long-term implications of early onset in bipolar disorder: Data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2004;55:875-881.

[49] Post RM, Leverich GS, Kupka RW, et al. Early-onset bipolar disorder and treatment delay are risk factors for poor outcome in adulthood. J Clin Psychiatry 2010;71:864-872.

[50] Axelson D, Birmaher B, Strober M, et al. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch Gen Psychiatry 2006;63: 139-1148.

[51] Findling RL, Gracious BL, McNamara NK, et al. Rapid, continuous cycling and psychiatric co-morbidity in pediatric bipolar I disorder. Bipolar Disorders 2001;3:202-210.

[52] Song M, Yoon H, Choi I, Hong SD, Joung YS. Differences of clinical characteristics and phenotypes between prepubertal- and adolescent-onset bipolar disorders. J Korean Med Sci 2010;25:912-917.

[53] Duffy A, Alda M, Hajek T, Sherry SB, Grof P. Early stages in the development of bipolar disorder. J Affect Disord 2010;121:127-135.

[54] Lapalme M, Hodgins S, LaRoche C. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. Can J Psychiatry 1997; 42: 623-631.

[55] Craig TJ, Ye Q, Bromet EJ. Mortality among first-admission patients with psychosis. Comprehensive Psychiatry 2006;47:246-251.

[56] Hoyer EH, Mortensen PB, Olesen AV. Mortality and causes of death in a total national sample of patients with affective disorders admitted for the first time between 1973 and 1993. Br J Psychiatry 2000;176:76-82.

[57] Osby U, Brandt L, Correia N, Ekbom A. Sparen P. Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 2001;58:844-850.

[58] Harris EC and Barraclough B. Excess mortality of mental disorder. Br J Psychiatry 1998;173:11-53.

[59] Carney CP and Jones LE. Medical comorbidity in women and men with bipolar disorders: A population-based controlled study. Psychosomatic Medicine 2006;68:684-691.

[60] Krishnan KRR. Psychiatric and medical comorbidities of bipolar disorder. Psychomsomatic Medicine 2005;67:1-8.

[61] Tondo L, Isacsson G, Baldessarini RJ. Suicidal behavior in bipolar disorder - Risk and prevention. CNS Drugs 2003;17(7):491-511.

[62] Harris EC and Barraclough B. Suicide as an outcome for mental disorders. Br J Psychiatry 1997;170:205-228.

[63] Baldessarini R and Tondo L. Suicide risk and treatments for patients with bipolar disorder. JAMA 2003;290:1517 1519.

[64] Marco CA and Vaughan J. Emergency management of agitation in schizophrenia. Am J Emerg Med 2005;23:767-776.

[65] Dickey B, Normand S-LT, Weiss RD, Drake RE, Azeni H. Medical morbidity, mental illness, and substance use disorders. Psychiatr Serv 2002;53:861-867.

[66] Newcomer JW. Medical risk in patients with bipolar disorder and schizophrenia. J Clin Psychiatry 2006;67(Suppl 9):25 30.

[67] McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant status and methodology. BMC Med 2004;2:13.

[68] Kirkbride JB, Fearon P, Morgan C, et al. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: Findings from the 3-center AESOP study. Arch Gen Psychiatry 2006;63:250-258.

[69] Boydell J, van Os J, Lambri M, et al. Incidence of schizophrenia in south-east London between 1965 and 1997. Br J Psychiatry 2003;182:45-49.

[70] Amminger G, Harris M, Conus P, et al. Treated incidence of first-episode psychosis in the catchment area of EPPIC between 1997 and 2000. Acta Psychiatr Scand 2006;114:337-345.

[71] Jablensky A, Sartorius N, Ernberg G, et al. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. Psychol Med Monogr Suppl 1992;20:1-97.

[72] Jablensky A. The 100-year epidemiology of schizophrenia. Schizophr Res 1997;28:111-125.

[73] Goldner EM, Hsu L, Waraich P, Somers JM. Prevalence and incidence studies of schizophrenic disorders: A systematic review of the literature. Can J Psychiatry 2002;47:833-843.

[74] Suvisaari JM, Haukka J, Tanskanen A, Lonnqvist JK. Age at onset and outcome in schizophrenia are related to the degree of familial loading. Br J Psychiatry 1998;173:494-500.

[75] Takei N, Lewis G, Sham PC, Murray RM. Age-period-cohort analysis of the incidence of schizophrenia in Scotland. Psychol Med 1996;26:963-973.

[76] Preti A and Miotto P. Increase in first admissions for schizophrenia and other major psychoses in Italy. Psychiatry Res 2000;94:139-152.

[77] Tsuchiya KJ and Munk-Jorgensen P. First-admission rates of schizophrenia in Denmark, 1980-1997: Have they been increasing? Schizophr Res 2002;54:187-191.

[78] Bray I, Waraich P, Jones W, et al. Increase in schizophrenia incidence rates: Findings in a Canadian cohort born 1975-1985. Soc Psychiatry Psychiatr Epidemiol 2006;41:611-618.

[79] Volavka J, Laska E, Baker S, et al. History of violent behaviour and schizophrenia in different cultures. Analyses based on the WHO study on determinants of outcome of severe mental disorders. Br J Psychiatry 1997;171:9-14.

[80] Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med 2005;2:e141.

[81] San L, Arranz B, Escobar R. Pharmacological management of acutely agitated schizophrenic patients. Curr Pharm Des 2005;11:2471-2477.

[82] Mohr P, Pecenak J, Svestka J, Swingler D, Treuer T. Treatment of acute agitation in psychotic disorders. Neuro Endocrinol Lett 2005;26:327-335.

[83] Nolan KA, Volavka J, Czobor P, et al. Aggression and psychopathology in treatment-resistant inpatients with schizophrenia and schizoaffective disorder. J Psychiatr Res 2005;39:109-115.

[84] Swanson J, Swartz M, Van Dorn R, et al. A national study of violent behavior in persons with schizophrenia. Arch Gen Psychiatry 2006;63:490-499.

[85] Bebbington PE, Angermeyer M, Azorin JM, et al. The European Schizophrenia Cohort (EuroSC): A naturalistic prognostic and economic study. Soc Psychiatry Psychiatr Epidemiol 2005;40:707-71.

[86] Beitchman JH. Childhood schizophrenia. A review and comparison with adult-onset schizophrenia. Psychiatr Clin North Am 1985;8:793-814.

[87] Remschmidt HE, Schulz E, Martin M, Warnke A, Trott GE. Childhood-onset schizophrenia: History of the concept and recent studies. Schizophr Bull 1994;20:727-745.

[88] Hafner H and Nowotny B. Epidemiology of early-onset schizophrenia. Eur Arch Psychiatry Clin Neurosci 1995;245:80-92.

[89] Eggers C and Bunk D. The long-term course of childhood-onset schizophrenia: A 42-year followup. Schizophr Bull 1997;23:105-117.

[90] Hafner H. Gender differences in schizophrenia. Psychoneuroendocrinology 2003;28(Suppl 2):17-54.

[91] Aleman A, Kahn RS, Selten J-P. Sex differences in the risk of schizophrenia. Arch Gen Psychiatry 2003;60:565-571.

[92] Salem J and Kring A. The role of gender differences in the reduction of etiologic heterogeneity in schizophrenia. Clinical Psychology Review 1998;18:795-819.

[93] Leung A and Chue P. Sex differences in schizophrenia, a review of the literature. Acta Psychiatr Scand 2000;101:3-38.

[94] Castle D, Sham P, Murray R. Differences in distribution of ages of onset in males and females with schizophrenia. Schizophrenia Research 1998;33:179-183.

[95] Riecher-Rossler A and Hafner H. Gender aspects in schizophrenia: Bridging the border between social and biological psychiatry. Acta Psychiatr Scand Suppl 2000;(407):58-62.

[96] Rossler W, Salize HJ, van Os J, Riecher-Rossler A. Size of burden of schizophrenia and psychotic disorders. Eur Neuropsychopharmacol 2005;15:399-409.

[97] Moriarty P, Lieber D, Bennett A, et al. Gender differences in poor outcome patients with lifelong schizophrenia. Schizophr Bull 2001;27:103-113.

[98] Cantor-Graae E and Selten J-P. Schizophrenia and migration: A meta-analysis and review. Am J Psychiatry 2005;162:12-24.

[99] Smith GN, Boydell J, Murray RM, et al. The incidence of schizophrenia in European immigrants to Canada. Schizophr Res 2006;87:205-211.

[100] Leao TS, Sundquist J, Frank G, et al. Incidence of schizophrenia or other psychoses in first- and second-generation immigrants: A national cohort study. J Nerv Ment Dis 2006;194:27-33.

[101] Veling W, Selten J-P, Veen N, et al. Incidence of schizophrenia among ethnic minorities in the Netherlands: A four-year first-contact study. Schizophrenia Research 2006;86:189-193.

[102] Selten JP, Cantor-Graae E, Kahn RS. Migration and schizophrenia. Curr Opin Psychiatry 2007;20:111-115.

[103] Pedersen CB and Mortensen PB. Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. Arch Gen Psychiatry 2001;58:1039-1046.

[104] Hopper K and Wanderling J. Revisiting the developed versus developing country distinction in course and outcome in schizophrenia: Results from ISoS, the WHO collaborative followup project. International Study of Schizophrenia. Schizophr Bull 2000;26:835-8

[105] Sartorius N, Gulbinat W, Harrsion G, Laska E, Siegel C. Long-term follow-up of schizophrenia in 16 countries: A description of the International Study of Schizophrenia conducted by the World Health Organization. Soc Psychiatry Psychiatr Epidemiol 1996;31

[106] Craig TJ, Siegel C, Hopper K, Lin S, Sartorius N. Outcome in schizophrenia and related disorders compared between developing and developed countries. A recursive partitioning re-analysis of the WHO DOSMD data. Br J Psychiatry 1997;170:229-233.

[107] Patel V, Cohen A, Thara R, Gureje O. Is the outcome of schizophrenia really better in developing coutnries? Rev Bras Psiquiatr 2006;28:149-152.

[108] Bromet EJ and Fennig S. Epidemiology and natural history of schizophrenia. Biol Psychiatry 1999;46:871-881.

[109] Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: Historical and meta-analytic review. Am J Psychiatry 2002;159:1080-1092.

[110] Verdoux H, Geddes JR, Takei N, et al. Obstetric complications and age at onset in schizophrenia: an international collaborative meta-analysis of individual patient data. Am J Psychiatry 1997;154:1220-1227.

[111] Geddes JR and Lawrie SM. Obstetric complications and schizophrenia: A meta-analysis. Br J Psychiatry 1995;167:786-79.

[112] Hultman C, Sparen P, Takei N, Murray R, Cnattingius S. Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: Case-control study. BMJ 1999;318:421-426.

[113] Sipos A, Rasmussen F, Harrison G, et al. Paternal age and schizophrenia: A population based cohort study. BMJ 2004;329:1070-1074.

[114] Dalman C and Allebeck P. Paternal age and schizophrenia: Further support for an association. Am J Psychiatry 2002;159:1591-1592.

[115] Byrne M, Agerbo E, Ewald H, Eaton WW, Mortensen PB. Parental age and risk of schizophrenia. Arch Gen Psychiatry 2003;60:673-678.

[116] El-Saadi O, Pedersen CB, McNeil TF, et al. Paternal and maternal age as risk factors for psychosis: Findings from Denmark, Sweden and Australia. Schizophrenia Research 2004;67:227-236.

[117] Wohl M and Gorwood P. Paternal ages below or above 35 years old are associated with a different risk of schizophrenia in the offspring. Eur Psychiatry 2007;22:22-26.

[118] Brown A. Prenatal infection as a risk factor for schizophrenia. Schizophrenia Bulletin 2006;32:200-202.

[119] Reichenberg A, Weiser M, Rapp MA, et al. Elaboration on premorbid intellectual performance in schizophrenia: Premorbid intellectual decline and risk for schizophrenia. Arch Gen Psychiatry 2005;62:1297-1304.

[120] Brown S. Excess mortality of schizophrenia. A meta-analysis. Br J Psychiatry 1997;171:502-508.

[121] Joukamaa M, Heliovaara M, Knekt P, et al. Mental disorders and cause-specific mortality. Br J Psychiatry 2001;179:498-502

[122] Braga RJ, Petrides G, Figueira I. Anxiety disorders in schizophrenia. Compr Psychiatry 2004;45:460-468.

[123] Tibbo P, Swainson J, Chue P, LeMelledo JM. Prevalence and relationship to delusions and hallucinations of anxiety disorders in schizophrenia. Depress Anxiety 2003;17:65-72.

[124] Pallanti S, Quercioli L, Hollander E. Social anxiety in outpatients with schizophrenia: A relevant cause of disability. Am J Psychiatry 2004;161:53-58.

[125] Turnbull G and Bebbington P. Anxiety and the schizophrenic process: Clinical and epidemiological evidence. Soc Psychiatry Psychiatr Epidemiol 2001;36:235-243.

[126] Wong VCN and Hui SLH. Epidemiological study of autism spectrum disorder in China. J Child Neurol 2008;23:67-72.

[127] Williams JG, Higgins JPT, Brayne CEG. Systematic review of prevalence studies of autism spectrum disorders. Arch Dis Child 2006;91:8-15.

[128] Simon GE, Goldberg DP, Von Korff M, Ustun TB. Understanding cross-national differences in depression prevalence. Psychol Med 2002;32:585-594.

[129] Chang SM, Hahm BJ, Lee JY, et al. Cross-national difference in the prevalence of depression caused by the diagnostic threshold. J Affect Disord 2008;106:159-167.

[130] Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003;289:3095-3105.

[131] Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: Results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry 2005;62:1097-1106.

[132] Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA 1996;276:293-299.

[133] Andrade L, Caraveo-Anduaga JJ, Berglund P, et al. The epidemiology of major depressive episodes: Results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. Int J Methods Psychiatr Res 2003;12:3-21.

[134] Moussavi S, Chatterji S, Verdes E, et al. Depression, chronic diseases, and decrements in health: Results from the World Health Surveys. Lancet 2007;370:851-858.

[135] Haarasilta L, Marttunen M, Kaprio J, Aro H. The 12-month prevalence and characteristics of major depressive episode in a representative nationwide sample of adolescents and young adults. Psychol Med 2001;31:1169-1179.

[136] Kessler RC, Gruber M, Hettema JM, et al. Co-morbid major depression and generalized anxiety disorders in the National Comorbidity Survey follow-up. Psychol Med 2008;38:365-37.

[137] Lee S, Tsang A, Huang Y-Q, et al. The epidemiology of depression in metropolitan China. Psychol Med 2009;39:735-747.

[138] Friedlander AH and Mahler ME. Major depressive disorder. Psychopathology, medical management and dental implications. J Am Dent Assoc 2001;132:629-638.

[139] Eaton WW, Shao H, Nestadt G, et al. Population-based study of first onset and chronicity in major depressive disorder. Arch Gen Psychiatry 2008;65:513-520.

[140] Pettit JW, Lewinsohn PM, Joiner TE Jr. Propagation of major depressive disorder: Relationship between first episode symptoms and recurrence. Psychiatry Res 2006;141:271-278.

[141] Keller MB. Issues in treatment-resistant depression. J Clin Psychiatry 2005;66(Suppl 8):5-12.

[142] Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. J Clin Psychiatry 2006;67(Suppl 6): 16-22.

[143] Fava M and Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19: 179-20.

[144] Kornstein SG, Schneider RK (2001) Clinical features of treatment-resistant depression. J Clin Psychiatry 1996;62(Suppl 16):18-25.

[145] Akiskal HS, Benazzi F, Perugi G, Rihmer Z. Agitated "unipolar" depression reconceptualized as a depressive mixed state: Implications for the antidepressant-suicide controversy. J Affect Disord 2005;85:245-258.

[146] Patten SB, Wang JL, Williams JV, et al. Descriptive epidemiology of major depression in Canada. Can J Psychiatry 2006;51:84-90.

[147] Angst J, Gamma A, Gastpar M, et al. Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies. Eur Arch Psychiatry Clin Neurosci 2002;252:201-209.

[148] Marcus SM, Kerber KB, Rush AJ, et al. Sex differences in depression symptoms in treatment-seeking adults: Confirmatory analyses from the Sequenced Treatment Alternatives to Relieve Depression study. Compr Psychiatry 2008;49:238-246.

[149] Marcus SM, Young EA, Kerber KB, et al. Gender differences in depression: Findings from the STAR*D study. J Affect Disord 2005;87:141-150.

[150] Romans SE, Tyas J, Cohen MM, Silverstone T. Gender differences in the symptoms of major depressive disorder. J Nerv Ment Dis 2007;195:905-911.

[151] Moskvina V, Farmer A, Jones IR, et al. Sex differences in symptom patterns of recurrent major depression in siblings. Depress Anxiety 2008;25:527-534.

[152] Zisook S, Lesser I, Stewart JW, et al. Effect of age at onset on the course of major depressive disorder. Am J Psychiatry 2007;164:1539-1546.

[153] Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: Review and meta-analysis. Am J Psychiatry 2000;157:1552-1562.

[154] Tozzi F, Prokopenko I, Perry JD, et al. Family history of depression is associated with younger age of onset in patients with recurrent depression. Psychol Med 2008;38:641-649.

[155] Williams DR, Gonzalez HM, Neighbors H, et al. Prevalence and distribution of major depressive disorder in African Americans, Caribbean blacks, and non-Hispanic whites: Results from the National Survey of American Life. Arch Gen Psychiatry 2007;64:305-315.

[156] Wang JL. Rural-urban differences in the prevalence of major depression and associated impairment. Soc Psychiatry Psychiatr Epidemiol 2004;39:19-25.

[157] Wulsin LR, Vaillant GE, Wells VE. A systematic review of the mortality of depression. Psychosom Med 1999;61:6-17.

[158] Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry 2007;29:147-155.

[159] Chapman DP, Perry GS, Strine TW. The vital link between chronic disease and depressive disorders. Prev Chronic Dis 2005;2(1):1-10.

[160] Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res 2009;65:591-598.

[161] Honda H, Shimizu Y, Imai M, Nitto Y. Cumulative incidence of childhood autism: A total population study of better accuracy and precision. Dev Med Child Neurol 2005;47:10-18.

[162] Atladottir HO, Parner ET, Schendel D, Dalsgaard S, Thomsen PH, Thorsen P. Time trends in reported diagnoses of childhood neuropsychiatric disorders: A Danish cohort study. Arch Pediatr Adolesc Med 2007;161:193-198.

[163] Lauritsen MB, Pedersen CB, Mortensen PB. The incidence and prevalence of pervasive developmental disorders: A Danish population-based study. Psychol Med 2004;34:1339-1346.

[164] Williams K, Glasson EJ, Wray J, et al. Incidence of autism spectrum disorders in children in two Australian states. Med J Aust 2005;182:108-111.

[165] Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. The incidence of autism in Olmsted County, Minnesota, 1976-1997: Results from a population-based study. Arch Pediatr Adolesc Med 2005;159:37-44.

[166] Powell JE, Edwards A, Edwards M, Pandit BS, Sungum-Paliwal SR, Whitehouse W. Changes in the incidence of childhood autism and other autistic spectrum disorders in preschool children from two areas of the West Midlands, UK. Dev Med Child Neurol 2000;42:624

[167] Posserud M-B, Lundervold AJ, Gillberg C. Autistic features in a total population of 7-9-year-old children assessed by the ASSQ (Autism Spectrum Screening Questionnaire). J Child Psychol Psychiatry 2006;47:167-175.

[168] Hughes JR. Update on autism: A review of 1300 reports published in 2008. Epilepsy Behav 2009;16:569-589.

[169] Williams K, MacDermott S, Ridley G, Glasson EJ, Wray JA. The prevalence of autism in Australia. Can it be established from existing data? J Paediatr Child Health 2008;44:504-510.

[170] Kogan MD, Blumberg SJ, Schieve LA, et al. Prevalence of parent-reported diagnosis of autism spectrum disorder among children in the US, 2007. Pediatrics 2009;124:1395-1403.

[171] Centers for Disease Control. Prevalence of autism spectrum disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. MMWR Surveill Summ 2009;58:1-20.

[172] Kim YS, Leventhal BL, Koh Y-J et al. Prevalence of Autism Spectrum Disorders in a Total Population Sample. Am J Psychiatry 2011;168:904-912.

[173] Santangelo SL and Tsatsanis K. What is known about autism: Genes, brain, and behavior. Am J Pharmacogenomics 2005;5:71-92.

[174] Mouridsen SE, Bronnum-Hansen H, Rich B, Isager T. Mortality and causes of death in autism spectrum disorders: An update. Autism 2008;12:403-414.

[175] Gillberg C, Billstedt E, Sundh V, Gillberg IC. Mortality in autism: A prospective longitudinal community-based study. J Autism Dev Disord 2010;40:352-357.

[176] Pickett JA, Paculdo DR, Shavelle RM, Strauss DJ. 1998-2002 Update on "Causes of death in autism." J Autism Dev Disord 2006;36:287-288.

[177] Pickett J, Xiu E, Tuchman R Dawson G, Lajonchere C. Mortality in individuals with autism, with and without epilepsy. J Child Neurol 2011;26:932-939.

[178] Module 2.7.4, clinical summary of safety: Aripiprazole in the treatment of bipolar I disorder, manic or mixed. Bristol-Myers Squibb Pharmaceutical Research Institute; 2007. Document Control No. 930022290.

[179] Khan M and Farver D. Recognition, assessment, and management of neuroleptic malignant syndrome. SDJ Med 2000;53:395-400.

[180] Gurrera RJ, Simpson JC, Tsuang MT. Meta-analytic evidence of systematic bias in estimates of neuroleptic malignant syndrome incidence. Comprehensive Psychiatry 2007;48:205-211.

[181] Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. Am J Psychiatry 2007;16:4870-4876.

[182] Ananth J, Parameswaran S, Gunatilake S, Burgoyne K, Sidhom T. Neuroleptic malignant syndrome and atypical antipsychotic drugs. J Clin Psychiatry 2004;65:464-470.

[183] Jones M., Swain J., DeLisle F., Kryzhanovskaya L., Kinon B.J. Risk of seizures among patients with schizophrenia as compared to the general population in the clinical practice research datalink (CPRD). Pharmacoepidemiology and Drug Safety. Conference: 29t

[184] Jones M.E., Rizvi L.A., Strombom I., DeLisle F., Kryzhanovskaya L., Wernicke J., Kinon B.J. Exploratory analysis of the relationship between antipsychotic use and the incidence of seizures among patients with schizophrenia in the UK General Practice Resea

[185] Gelisse P, Samuelian JC, Genton P. Is schizophrenia a risk factor for epilepsy or acute symptomatic seizures? Epilepsia 1999;40:1566-1571.

[186] Levisohn PM. The autism-epilepsy connection. Epilepsia 2007;48(Suppl 9):33-35. (279)

[187] Matsuo M, Maeda T, Sasaki K, Ishii K, Hamasaki Y. Frequent association of autism spectrum disorder in patients with childhood onset epilepsy. Brain Dev 2010;32:759-763. (280)

[188] Canitano R. Epilepsy in autism spectrum disorders. Eur Child Adolesc Psychiatry 2007;16:61-66. (281

[189] Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects – A comprehensive literature review. CNS Drugs 2005;19(Supp 1):1-93.

[190] McIntrye RS, Konarski JZ, Misener VL, et al. Bipolar disorder and diabetes mellitis: Epidemiology, etiology, and treatment implications. Annals of Clinical Psychiatry 2005;17(2):83-9.

[191] Guo JJ, Keck PE Jr, Corey-Lisle PK, et al. Risk of diabetes mellitus associated with atypical antipsychotic use among patients with bipolar disorder: A retrospective, population-based, case-control study. J Clin Psychiatry 2006;67:1055-1061.

[192] Guo JJ, Keck PE Jr, Corey-Lisle PK, et al. Risk of diabetes mellitus associated with atypical antipsychotic use among Medicaid patients with bipolar disorder: A nested case-control study. Pharmacotherapy 2007;27:(1):27-35.

[193] van Winkel R, De Hert M, Van Eyck D, et al. Screening for diabetes and other metabolic abnormalities in patients with schizophrenia and schizoaffective disorder: Evaluation of incidence and screening methods. J Clin Psychiatry 2006;67:1493-150.

[194] Henderson DC. Schizophrenia and comorbid metabolic disorders. J Clin Psychiatry 2005;66(Suppl 6):11-20.

[195] Weber B, Schweiger U, Deuschle M, Heuser I. Major depression and impaired glucose tolerance. Exp Clin Endocrinol Diabetes 2000;108:187-190.

[196] Knol MJ, Twisk JW, Beekman AT, et al. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. Diabetologia 2006;49:837-845.

[197] Brown LC, Majumdar SR, Newman SC, Johnson JA. History of depression increases risk of type 2 diabetes in younger adults. Diabetes Care 2005;28:1063-1067.

[198] Jerrell JM, McIntyre RS, Tripathi A. A cohort study of the prevalence and impact of comorbid medical conditions in pediatric bipolar disorder. J Clin Psychiatry 2010;71:1518-1525.

[199] Panagiotopoulos C, Ronsley R, Davidson J. Increased prevalence of obesity and glucose intolerance in youth treated with second-generation antipsychotic medications. Can J Psychiatry 2009;54:743-749.

[200] Angst J. Clinical course of affective disorders. In: Depressive illness. Prediction of course and outcome. Helgason T and Daley RJ eds, Springer-Verlag, Berlin: Germany, 1988, pp 1-44.

[201] Gonzalez-Pinto A, Mosquera F, Alonso M, Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment. Bipolar Disorders 2006;8:618-624.

[202] Marangell LB, Bauer MS, Dennehy EB, et al. Prospective predictors of suicide and suicide attempts in 1,556 patients with bipolar disorders followed for up to 2 years. Bipolar Disorders 2006;8:566-575.

[203] Goodwin FK, Fireman B, Simon GE, Suicide risk in bipolar disorder during treatment with lithium and divalproex. JAMA 2003;290:1467-1473.

[204] Goodwin FK, Jamison KR, Goodwin F. Suicide. In: Manic-depressive illness. Oxford University Press, New York: New York, 1990, Chapter 10, pp 227-244.

[205] Ulcickas Yood, M., DeLorenze, G., Quesenberry, C. P., Tsai, A. L., Phillips, S., Willey, V. J., & Oliveria, S. A. Epidemiologic study of aripiprazole use and the incidence of suicide events. Pharmacoepidemiology and drug safety, 2010; 19(11): 1124-1130.

[206] Caetano SC, Olvera RL, Hunter K, et al. Association of psychosis with suicidality in pediatric bipolar I, II and bipolar NOS patients. J Affect Disord 2006;91:33-37.

[207] Dilsaver SC, Benazzi F, Rihmer Z, Akiskal KK, Akiskal HS. Gender, suicidality and bipolar mixed states in adolescents. J Affect Disord 2005;87:11-16.

[208] Goldstein TR, Birmaher B, Axelson D, et al. History of suicide attempts in pediatric bipolar disorder: Factors associated with increased risk. Bipolar Disord 2005;7:525-53.

[209] Guile J.M., Brunelle J., Consoli A., Bodeau N., Cohen D. Bipolar disorder type i and suicide attempts in adolescence: Data from a follow-up study. Adolescent Psychiatry. Conference: 2011 ISAPP Congress Berlin Germany. 2-12; 2 (1) (pp 88)

[210] Mauri, M C; Paletta, S; Maffini, M; Moliterno, D; Altamura, A C. Suicide attempts in schizophrenic patients: clinical variables. Asian Journal of Psychiatry. 2013; 6(5):421-7

[211] Caldwell C and Gottesman I. Schizophrenics kill themselves too: A review of risk factors for suicide. Schizophrenia Bulletin 1990;16:571-58.

[212] Palmer BA, Pankratz S, Bostwick JM. The lifetime risk of suicide in schizophrenia: A reexamination. Arch Gen Psychiatry 2005;62:247-253.

[213] Krausz M, Muller-Thomsen T, Haasen C. Suicide among schizophrenic adolescents in the long-term course of illness. Psychopathology 1995;28:95-103.

[214] Shoval G, Sever J, Sher L, et al. Substance use, suicidality, and adolescent-onset schizophrenia: An Israeli 10-year retrospective study. J Child Adolesc Psychopharmacol 2006;16:767-775.

[215] WHO Report 2001 on mental health: New understanding, new hope. Available at: http://www.who.int/whr/2001/en/index.html. Accessed 16 October 200.

[216] McGirr A, Renaud J, Seguin M, et al. An examination of DSM-IV depressive symptoms and risk for suicide completion in major depressive disorder: A psychological autopsy study. J Affect Disord 2007;97:203-209.

[217] Aripiprazole response to CHMP 17-Nov-2005 list of questions. Bristol-Myers Squibb Company; 2006. Document Control No. 930014282.

[218] Kilbourne AM, Post EP, Bauer MS, et al. Therapeutic drug and cardiovascular disease risk monitoring in patients with bipolar disorder. J Affect Disord 2007;102:145-151.

[219] Cassidy F and Carroll BJ. Hypocholesterolemia during mixed manic episodes. Eur Arch Psychiatry Clin Neurosci 2002;252:110-11.

[220] Ghaemi SN, Shields GS, Hegarty JD, Goodwin FK. Cholesterol levels in mood disorders: High or low? Bipolar Disord 2000;2:60-64.

[221] Correll CU, Harris JL, Pantaleon Moya RA, et al. Low-density lipoprotein cholesterol in patients treated with atypical antipsychotics: Missed targets and lost opportunities. Schizophr Res 2007;92:103-107.

[222] Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: Findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord 2005;7:424-430.

[223] Musselman DL, Betan E, Larsen H, Phillips LS. Relationship of

depression to diabetes types 1 and 2: Epidemiology, biology, and
treatment. Biol Psychiatry 2003;54:317-329

[224] Meyer JM and Koro CE. The effects of antipsychotic therapy on serum lipids: A comprehensive review. Schizophr Res 2004;70:1-17.

[225] Casey DE. Dyslipidemia and atypical antipsychotic drugs. J Clin Psychiatry 2004;65(Suppl 18): 27-35.

[226] Sacks FM. Metabolic syndrome: Epidemiology and consequences. J Clin Psychiatry 2004;65(Suppl 18):3-12.

[227] Newcomer JW. Antipsychotic medications: Metabolic and cardiovascular risk. J Clin Psychiatry 2007;68(Suppl 4):8-13.

[228] Saari KM, Lindeman SM, Viilo KM, et al. A 4-fold risk of metabolic syndrome in patients with schizophrenia: The Northern Finland 1966 Birth Cohort study. J Clin Psychiatry 2005;66:559-563.

[229] Hagg S, Lindblom Y, Mjorndal T, Adolfsson R. High prevalence of the metabolic syndrome among a Swedish cohort of patients with schizophrenia. Int Clin Psychopharmacol 2006;21:93-98.

[230] Suvisaari JM, Saarni SI, Perala J, et al. Metabolic syndrome among persons with schizophrenia and other psychotic disorders in a general population survey. J Clin Psychiatry 2007;68:1045-1055.

[231] Leitao-Azevedo CL, Guimaraes LR, de Abreu MG, et al. Increased dyslipidemia in schizophrenic outpatients using new generation antipsychotics. Rev Bras Psiquiatr 2006;28:301-304.

[232] Heiskanen TH, Niskanen LK, Hintikka JJ, et al. Metabolic syndrome and depression: A cross-sectional analysis. J Clin Psychiatry 2006;67:1422-1427.

[233] Saari K, Lindeman S, Koponen H, Jokelainen J, Isohanni M. Higher serum triglyceride levels in early-onset schizophrenia. Am J Psychiatry 2004;161:176.

[234] Kumar, A., Datta, S. S., Wright, S. D., Furtado, V. A., & Russell, P. S. (2013). Atypical antipsychotics for psychosis in adolescents. The Cochrane Library, 2013: (10): 2.

[235] Yan H, Chen JD, Zheng XY. Potential mechanisms of atypical antipsychotic-induced hypertriglyceridemia. Psychopharmacology 2013;229:1–7.

[236] Citrome L, Kalsekar I, Baker RA, et al. A review of real-world data on the effects of aripiprazole on weight and metabolic outcomes in adults. Curr Med Res Opin. 2014;30(8):1629-41.

[237] Tarraf C, Naja WJ. Aripiprazole-Induced Hyperlipidemia: An Update. Prim Care Companion CNS Disord. 2016;18(4):doi:10.4088/PCC.16r01958

[238] Rummel-Kluge C, Komossa K, Schwarz S, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. Schizophr Res 2010;123:225-33.

[239] Tolliver BK, McRae AL, Verduin ML, et al. Reversible elevation of triglycerides in dual-diagnosis patients taking aripiprazole: a case series. J Clin Psychopharmacol 2008;28(4):464-7.

[240] McQuade RD, Stock E, Marcus R, et al. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. J Clin Psychiatry 2004;65(Suppl 18):47-56.

[241] Keck PE Jr, Calabrese JR, McIntyre RS, et al; Aripiprazole Study Group. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. J Clin Psychiatry 2007;68(10):1480-91.

[242] Kerwin R, Millet B, Herman E, et al. A multicentre, randomized, naturalistic, open-label study between aripiprazole and standard of care in the management of community-treated schizophrenic patients Schizophrenia Trial of Aripiprazole: (STAR) study. Eur P

[243] Takeuchi Y, Kajiyama K, Ishiguro C, et al. Atypical Antipsychotics and the Risk of Hyperlipidemia: A Sequence Symmetry Analysis. Drug Saf 2015;38(7):641-50.

[244] De Hert M, Hanssens L, van Winkel R, et al. A case series: evaluation of the metabolic safety of aripiprazole. Schizophr Bull 2007;33(3):823-30.

[245] Kim SW, Shin IS, Kim JM, et al. Effectiveness of switching to aripiprazole from atypical antipsychotics in patients with schizophrenia. Clin Neuropharmacol 2009;32(5):243-9.

[246] McIntyre RS; Jerrell JM. Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. Archives of Pediatrics & Adolescent Medicine. 2008; 162(10):929-35.

[247] Tan RS and Philip P. Orthostatic hypotension in the elderly. Part I: Role of drugs in etiology. Clinical Geriatrics 1998;6:37-57.

[248] Masaki KH, Schatz IJ, Burchfiel CM, et al. Orthostatic hypotension predicts mortality in elderly men: The Honolulu Heart Program. Circulation 1998;98:2290-2295.

[249] Mukai S and Lipsitz LA. Orthostatic hypotension. Clin Geriatr Med 2002;18:253-268.

[250] Frishman WH, Azer V, Sica D. Drug treatment of orthostatic hypotension and vasovagal syncope. Heart Dis 2003;5:49-64.

[251] Montastruc JL, Laborie K, Bagheri H, Senard JM. Drug-induced orthostatic hypotension: A five-year experience in a regional pharmacovigilance centre in France. Clin Drug Invest 1997;14:61-65.

[252] Module 2.7.4, clinical summary of safety: Aripiprazole in the treatment of acute schizophrenia. Bristol-Myers Squibb Pharmaceutical Research Institute; 2005. Document Control No. 930011197.

[253] Module 2.7.4, summary of clinical cafety: Adjunctive treatment in patients with major depressive disorder. Bristol-Myers Squibb Research and Development; 2008. Document Control No. 930032139.

[254] Module 2.7.4, clinical summary of safety: Intramuscular aripiprazole in the treatment of acute agitation. Bristol-Myers Squibb Pharmaceutical Research Institute; 2005. Document Control No. 93000920.

[255] Study 31-03-240: A multicenter, randomized, double-blind, placebo-controlled study of two fixed oral doses of aripiprazole (10 mg and 30 mg) in the treatment of child and adolescent patients, ages 10-17 years, with bipolar I disorder, manic or mixed episo

[256] Study 31-03-241: A multi-center, open-label, safety and tolerability study of flexible-dose oral aripiprazole (2 mg - 30 mg) in the treatment of adolescent patients with schizophrenia, and child and adolescent patients with bipolar I disorder, manic or mi

[257] Module 2.7.4, summary of clinical safety: Aripiprazole as adjunctive therapy to lithium or valproate for the recurrence prevention of bipolar I disorder. Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930045000.

[258] Module 2.7.4, summary of clinical safety: Aripiprazole in the treatment of irritability associated with autistic disorder. Bristol-Myers Squibb Research and Development; 2010. Document Control No. 930044855.

[259] Study 31-09-266: A Long-Term Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aripiprazole (OPC-14597) as Maintenance Treatment in Adolescent Patients with Schizophrenia. Clinical Study

[260] A Long-term, Multicenter, Open-Label Study to Evaluate the Safety and Tolerability of Flexible-Dose Oral Aripiprazole (OPC-14597) as Study 31-09-267: Maintenance Treatment in Adolescent Patients with Schizophrenia or Child and Adolescent Patients with Bip

[261] Study 31-12-293: A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder. Clinical Study Report. Otsuka.

[262] Study 31-12-294: An Open-Label, Multicenter Study Evaluating the Safety and Tolerability of Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder. Clinical Study Report. Otsuka.

[263] Study 31-97-303: An Open-Label Follow-on Study of the Long Term Safety of Aripiprazole in Patients with Chronic Schizophrenia. Clinical Study Report. Otsuka.

[264] Assessment of the In Vivo Release Characteristics and Safety of an Intramuscular Depot Formulation of Aripiprazole in Subjects with Schizophrenia or Schizoaffective Disorder. Clinical Study Report (CN138-020). Otsuka. 27-Jun-2007. BMS Document Control No.

[265] Assessment of the Safety, Tolerability, and Pharmacokinetics of Aripiprazole IM Depot Formulation by Single Administration in Patients with Schizophrenia (Clinical Pharmacology Trial). A Multicenter, Uncontrolled, Open-label, Single-dose Trial of OPC-1459

[266] An Open-label, Parallel Arm, Muliple Dose Tolerability, Pharmacokinetics and Safety Study in Adult Patients with Schizophrenia Following Administration of Aripiprazole Intramuscular (IM) Depot Formulatione Once Every Four Weeks. Amended Clinical Study Rep

[267] An Open-label, Safety and Tolerability Trial of Aripiprazole IM Depot Treatment Initiation in Adult Subjects with Schizophrenia Stabilized on Atypical Oral Antipsychotics Other than Aripiprazole. Clinical Study Summary (31-11-289). Otsuka. 29-Jun-2012.

[268] A 52-week, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular Depot Formulation of Aripiprazole (OPC-14597) as Maintenance Treatment in Patients with Schizophrenia. Amende

[269] A 38-week, Multicenter, Randomized, Double-blind, Active-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of an Intramuscular Depot Formulation of Aripiprazole (OPC-14597) as Maintenance Treatment in Patients with Schizophrenia. Clinica

[270] A 52-week, Multicenter, Open-label Study to Evaluate the Effectiveness of Aripiprazole Intramuscular Depot as Maintenance Treatment in Patients with Schizophrenia. Abbreviated Clinical Study Report (31-08-248). Otsuka. 10-Sep-2012.

[271] Open-label, multicenter, multiple dose trial to investigate the pharmacokinetics of aripiprazole IM depot (OPC-14597IMD) in patients with schizophrenia. Clinical Study Protocol Synopsis (031-10-002). Otsuka.

[272] A Multicenter, Open-label Study to Assess Hospitalization Rates in Adult Subjects with Schizophrenia Treated Prospectively for 6 Months with Aripiprazole IM Depot Compared with 6-month Retrospective Treatment with Oral Antipsychotics in a Naturalistic Com

[273] An Open-Label, Multicenter, Rollover, Long-term Study of Aripiprazole Intramuscular Depot in Patients with Schizophrenia. Abbreviated Clinical Study Report (31-10-270). Otsuka. 07-Sep-2012.

[274] Study 31-11-290: An Open-Label, Randomized, Parallel Arm, Bioavailability Trial of Aripiprazole IM Depot Administered in the Deltoid and Gluteal Muscle in Adult Subjects With Schizophrenia. Clinical Study Report. Otsuka.

[275] Study 31-12-298: Safety and Tolerability Study of Aripiprazole IM Depot in Adult Subjects With Schizophrenia. Clinical Study Report. Otsuka.

[276] Study 31-12-291: A 12 week, Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Aripiprazole Intramuscular Depot in the Acute Treatment of Adults with Schizophrenia. Clinical Study Report. Otsuka.

[277] Study 31-12-297: A 26-week Multicenter, Open-label, Extension Study of Aripiprazole Intramuscular Depot in Patients with Schizophrenia. Clinical Study Report. Otsuka.

[278] Trosch RM. Neuroleptic-induced movement disorders: Deconstructing extrapyramidal symptoms. J Amer Geriatrics Soc 2004;52:S266-S271.

[279] Pelonero AL, Levenson JL, Pandurangi AK. Neuroleptic malginant syndrome: A review. Psychiatric Services 1998;49:1163-1172.

[280] Gentile S. Extrapyramidal adverse events associated with atypical antipsychotic treatment of bipolar disorder. Journal of Clinical Psychopharmacology 2007;27(1):35-45.

[281] Mukherjee S, Rosen AM, Caracci G, et.al. Persistent tardive dyskinesia in bipolar patients. Arch General Psychiatry 1986;43:342-346.

[282] Ghadirian AM, Annable L, Belanger M, et al. A cross-sectional study of Parkinsonism and tardive dyskinesia in lithium-treated affective disordered patients. J Clin Psychiatry 1996;57:22-28.

[283] Akbostanci MC, Atbasoglu EC, Balaban H. Tardive dyskinesia, mild drug-induced dyskinesia, and drug-induced Parkinsonism: Risk factors and topographic distribution. Acta Neurol Belg 1999;99:176-181.

[284] Tenback D, van Harten P, Slooff C, van Os J. Evidence that early extrapyramidal symptoms predict later tardive dyskinesia: A prospective analysis of 10,000 patients in the European Schizophrenia Outpatient Health Outcomes (SOHO) Study. Am J Psychiatry 200

[285] Hedenmalm K, Guzey C, Dahl ML, Yue QY, Spigset O. Risk factors for extrapyramidal symptoms during treatment with selective serotonin reuptake inhibitors, including cytochrome P-450 enzyme, and serotonin and dopamine transporter and receptor polymorphisms.

[286] Kumra S, Oberstar JV, Sikich L, et al. Efficacy and tolerability of second-generation antipsychotics in children and pediatrics with schizophrenia. Schizophr Bull 2008;34: 60-71.

[287] Findling RL, Steiner H, Weller EB. Use of antipsychotics in children and pediatrics. J Clin Psychiatry 2005;66(Suppl 7):29-40.

[288] Armenteros JL and Davies M. Antipsychotics in early onset Schizophrenia: Systematic review and meta-analysis. Eur Child Adolesc Psychiatry 2006;15:141-148.

[289] Kane JM. Tardive dyskinesia circa 2006. Am J Psychiatry 2006:163(8):1316-1318.

[290] Kane JM, Woerner M, Lieberman J. Epidemiological aspects of tardive dyskinesia. L'Encephale 1988; XIV:191-194.

[291] Kane JM, Woerner M, Weinhold P, Wegner J, Kinon B. A prospective study of tardive dyskinesia development: Preliminary results. Journal of Clinical Psychopharmacology 1982:2(5):345-349.

[292] Van Rossum, I., Tenback, D., & van Os, J. Bipolar disorder and dopamine dysfunction: an indirect approach focusing on tardive movement syndromes in a naturalistic setting. BMC psychiatry, 2009; 9(1): 16-24.

[293] Hunt N and Silverstone T. Tardive dyskinesia in bipolar affective disorder: A catchment area study. International Clinical Psychopharmacology 1991;6:45-50.

[294] Sernyak MJ and Woods SW. Chronic neuroleptic use in manic-depressive illness. Psychopharmacology Bulletin 1993;29(3):375-38.

[295] Keck PE Jr, McElroy SL, Strakowski SM, Soutullo CA. Antipsychotics in the treatment of mood disorders and risk of tardive dyskinesia. J Clin Psychiatry 2000;61(Suppl 4):33-38.

[296] Miller, D. D., Eudicone, J. M., Pikalov, A., & Kim, E. Comparative assessment of the incidence and severity of tardive dyskinesia in patients receiving aripiprazole or haloperidol for the treatment of schizophrenia: a post hoc analysis. The Journal of cli

[297] Glazer W. Expected incidence of tardive dyskinesia associated with atypical antipsychotics. J Clin Psychiatry 2000;61(Suppl 4):21-26.

[298] Glazer W. Review of incidence studies of tardive dyskinesia associated with typical antipsychotics. J Clin Psychiatry 2000;61(Suppl 4):15-20.

[299] Nasrallah HA, Brecher M, Paulsson B. Placebo-level incidence of extrapyramidal symptoms (EPS) with quetiapine in controlled studies of patients with bipolar mania. Bipolar Disorders 2006;8:467-474.

[300] APA practice guidelines available at http:/www.spych.org/ psych_pract/treatg/pg/ SchizPG-Complete Feb94.pdf. Access 06 August 2001.

[301] Assessment of the Safety, Tolerability, and Pharmacokinetics of Aripiprazole IM Depot Formulation by Single Administration in Patients with Schizophrenia (Clinical Pharmacology Trial). A multicenter, uncontrolled, open-label, single-dose trial of OPC-1459

[302] A Multicenter, Open-label Study to Assess Hospitalization Rates in Adult Subjects With Schizophrenia Treated Prospectively for 6 Months With Aripiprazole IM Depot Compared With 6-month Retrospective Treatment With Oral Antipsychotics in a Naturalistic Com

[303] Mathias CH and Kimber JR. Postural hypotension: Causes, clinical features, investigation and management. Annu Rev Med 1999;50:317-336.

[304] Irvin DJ and White M. The importance of accurately assessing orthostatic hypotension. Geriatric Nursing 2004;25:99-10

[305] Buckley NA and Sanders P. Cardiovascular adverse effects of antipsychotic drugs. Drug Safety 2000;23:215-228.

[306] Tosato S, Albert U, Tomassi S, at al. A systematized review of atypical antipsychotics in pregnant women: balancing between risks of untreated illness and risks of drug-related adverse effects. J Clin Psychiatry. 2017; 78(5):e477-89.

[307] Grover S, Avasthi A, Sharma Y. Psychotropics in pregnancy: weighing the risks. Indian J Med Res. 2006; 123(4):497-512.

[308] Viguera AC, Nonacs R, Cohen LS,et al. Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry. 2000; 157(2):179-84.

[309] Viguera AC, Whitfield T, Baldessarini RJ, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am J Psychiatry. 2007; 164(12):1817-24; quiz 1923

[310] Freeman MP, Gelenberg AJ. Bipolar disorder in women: reproductive events and treatment considerations. Acta Psychiatr Scand. 2005; 112(2):88-96.

[311] Freeman MP, Smith KW, Freeman SA, et al. The impact of reproductive events on the course of bipolar disorder in women. J Clin Psychiatry. 2002; 63(4):284-7.

[312] Jablensky AV, Morgan V, Zubrick SR, et al. Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. Am J Psychiatry. 2005; 162:79-91.

[313] Bergink V, Bouvy PF, Vervoort JS, et al. Prevention of postpartum psychosis and mania in women at high risk. Am J Psychiatry 2012; 169: 609–615.

[314] Baldessarini RJ, Viguera AC. Neuroleptic withdrawal in schizophrenic patients. Arch Gen Psychiatry. 1995; 52(3):189-92.

[315] Robinson GE. Treatment of schizophrenia in pregnancy and postpartum. J Popul Ther Clin Pharmacol. 2012; 19(3):e380-6.

[316] Schneid-Kofman N, Sheiner E, Levy A. Psychiatric illness and adverse pregnancy outcome. Int J Gynaecol Obstet 2008; 101:53-6.

[317] Boden R, Lundgren M, Brandt L, et al. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. BMJ. 2012; 345:e7085.

[318] Hizkiyahu R, Levy A, Sheiner E. Pregnancy outcome of patients with schizophrenia. Am J Perinatol. 2010; 27:19-23.

[319] King-Hele S, Webb RT, Mortensen PB, et al. Risk of stillbirth and neonatal death linked with maternal mental illness: a national cohort study. Arch Dis Child Fetal Neonatal Ed. 2009; 94:F105-10.

[320] Vigod SN, Kurdyak PA, Dennis CL, et al. Maternal and newborn outcomes among women with schizophrenia: a retrospective population-based cohort study. BJOG 2014; 121:566-74.

[321] Howard LM. Fertility and pregnancy in women with psychotic disorders. Eur J Obstet Gynecol Reprod Biol. 2005; 119(1):3-10.

[322] Lin HC, Chen IJ, Chen YH, et al. Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference? Schizophr Res. 2010; 116:55-60.

[323] Bennedsen BE, Mortensen PB, Olesen AV, et al. Congenital malformations, stillbirths, and infant deaths among children of women with schizophrenia. Arch Gen Psychiatry. 2001; 58:674-9.

[324] MacCabe JH, Martinsson L, Lichtenstein P, et al. Adverse pregnancy outcomes in mothers with affective psychosis. Bipolar Disord. 2007; 9(3):305-9.

[325] Mei-Dan E, Ray JG, Vigod SN. Perinatal outcomes among women with bipolar disorder: a population-based cohort study. Am J Obstet Gynecol. 2015; 212(3):367.e1-8.

[326] Nguyen TN, Faulkner D, Frayne JS, et al. Obstetric and neonatal outcomes of pregnant women with severe mental illness at a specialist antenatal clinic. Med J Aust. 2013; 199 (3 Suppl):S26-9.

[327] Judd F, Komiti A, Sheehan P, et al. Adverse obstetric and neonatal outcomes in women with severe mental illness: to what extent can they be prevented? Schizophr Res. 2014; 157(1-3):305-9.

[328] Abel KM. Fetal antipsychotic exposure in a changing landscape: seeing the future. Br J Psychiatry. 2013; 202(5):321-3.

[329] Kulkarni J, Worsley R, Gilbert H, et al. A prospective cohort study of antipsychotic medications in pregnancy: the first 147 pregnancies and 100 one year old babies. PLoS One 2014; 9:e94788.

[330] Huybrechts KF, Hernández-Díaz S, Patorno E, et al. Antipsychotic Use in Pregnancy and the Risk for Congenital Malformations. JAMA Psychiatry. 2016; 73(9):938-46.

[331] Sadowski A, Todorow M, Yazdani Brojeni P, et al. Pregnancy outcomes following maternal exposure to second-generation antipsychotics given with other psychotropic drugs: a cohort study. BMJ Open 2013; 3(7).e003062.

[332] Bellet F, Beyens MN, Bernard N, et all. Exposure to aripiprazole during embryogenesis: a prospective multicenter cohort study. Pharmacoepidemiol Drug Saf. 2015; 24:368-80.

[333] Payne JL. Psychopharmacology in Pregnancy and Breastfeeding. Psychiatr Clin North Am. 2017; 40(2):217-38.

[334] Robakis T, Williams KE. Atypical antipsychotics during pregnancy. Curr Psychiatry. 2013: 12(7):13-20.

[335] Trixler M, Gáti A, Fekete S, et al. Use of antipsychotics in the management of schizophrenia during pregnancy. Drugs. 2005; 65(9):1193-206.

[336] Cohen LS, Viguera AC, McInerney KA, et al. Reproductive Safety of Second-Generation Antipsychotics: Current Data From the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. Am J Psychiatry. 2016; 173(3):263-70.

[337] Petersen I, McCrea RL, Sammon CJ, et al. Risks and benefits of psychotropic medication in pregnancy: cohort studies based on UK electronic primary care health records. Health Technol Assess. 2016; 20(23):1-176.

[338] Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002; 39(12):1890-900.

[339] Fulton D, Saleeb S. Pathophysiology and clinical features of isolated ventricular septal defects in infants and children. https://www.uptodate.com/contents/pathophysiology-and-clinical-features-of-isolated-ventricular-septal-defects-in-infants-and-childre

[340] Habermann F, Fritzsche J, Fuhlbrück F, et al. Atypical antipsychotic drugs and pregnancy outcome: a prospective, cohort study. J Clin Psychopharmacol. 2013; 33(4):453-62.

[341] Cohen LS, Viguera AC, McInerney KA, et al. Establishment of the National Pregnancy Registry for Atypical Antipsychotics. J Clin Psychiatry. 2015; 76(7):986-9.

[342] Cohen(1) L, Viguera A, Freeman M, et al. The national pregnancy registry for atypical antipsychotics: Effects of first trimester exposure to aripiprazole and quetiapine on risk for major malformations. Neuropsychopharmacol. 2016; 41(1 Suppl.): S496.

[343] Weiden PJ. EPS profiles: The atypical antipsychotics are not all the same. J Psychiatric Practice 2007;13(1):13-24