THE METABOLIC SYNDROME IN OUTPATIENTS WITH PSYCHOSIS: A COMPARATIVE STUDY BETWEEN LONG ACTING INJECTABLE OLANZAPINE AND RISPERIDONE

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Abstract

Context. Literature shows that patients taking antipsychotic medication risk developing metabolic complications.

Objective. The study aims to compare the presence of the metabolic syndrome (MS) and its components in outpatients treated with long acting injectable (LAI) olanzapine and risperidone.

Design. A double-center study was performed on outpatients with psychosis, which were divided into two samples: one treated with olanzapine and another with risperidone.

Subjects and Methods. The following data were analyzed: age, gender, severity of psychiatric symptoms, blood pressure, waist circumference, fasting blood glucose, lipid profile, tobacco use, medication, and time intervals related to psychosis duration (pre-LAI and LAI treatment).

Results. The study included 77 patients with schizophrenia and schizoaffective disorder. MS was present in 45 (58.4%) patients. Subjects with MS and abdominal obesity had higher durations of psychosis and of LAI treatment. Patients with hypertension had a higher pre-LAI treatment interval. Risperidone was associated with higher rates of hypertension and higher values of abdominal circumference than olanzapine.

Conclusions. The presence of MS is related to the duration of the psychosis and the time spent on LAI treatment with no differences between olanzapine and risperidone. Hypertension may be a consequence of age, disorder induced stress, or of treatment with risperidone.

Key words: metabolic syndrome, long acting injectable, olanzapine, risperidone.

INTRODUCTION

In patients suffering from chronic psychotic disorders, a long-term treatment is required. The lack of disorder insight makes patients with schizophrenia

and related psychoses less adherent to treatment (1), favoring recurrences and treatment resistance. In this respect, the use of long acting antipsychotic medication may improve the long-term prognosis. Another advantage offered by these formulations, in comparison with oral antipsychotics, is a lower yet efficient and less fluctuating serum concentration of the active substance. Nevertheless, a long-term treatment implies both benefits and risks.

Literature data show that, after age adjustment, patients with schizophrenia have a higher prevalence of metabolic diseases in comparison with the general population (2). This is important because the metabolic syndrome (MS) was associated in the general population with a 4 times relative risk for diabetes mellitus (3) and a relative risk of 1.78 for developing cardiovascular events or deaths (4). Antipsychotic medication acting directly on the hypothalamus or on the pancreatic Langerhans cells has an impact on the energetic metabolism. Patients with a first episode of psychosis don't have an average higher weight than the general population, but antipsychotic treatment either with conventional or atypical drugs may result in weight gain (5). Nevertheless, retrospective (6) and prospective (7) studies revealed that metabolic dysfunctions were present in patients with psychotic disorders both before and after the use of antipsychotics. The psychotic disorder, through its negative symptoms, affects patients' lifestyle (diet and activities) and may represent an independent risk factor for diabetes mellitus or low glucose tolerance (8). Obesity was found to be by 1.5 to 2 times more frequent in patients with schizophrenia than in the general population (9). The prevalence of hypertension is similar in patients with schizophrenia as in general population (10). The accumulated literature on antipsychotic metabolic effects has noted less impact on blood pressure than

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other metabolic parameters, a result that we confirm in this research (11).

The aim of the present study is to compare the presence of the MS and its components in outpatients with psychosis treated with long acting injectable (LAI) olanzapine and risperidone.

SUBJECTS AND METHODS

We conducted a cross-sectional study in outpatients with schizophrenia and schizoaffective disorder treated in ambulatory settings from two Romanian centers: Timisoara and Cluj. The subjects were divided into two samples according to the received treatment: olanzapine and risperidone. In order to assure treatment adherence and avoid pharmacokinetic discrepancies related to diverse formulations, only patients on LAI antipsychotics were included in the study. To ensure a stable antipsychotic blood level, the subjects had to be treated with LAI antipsychotics for at least 2 months. Two different second generation antipsychotics were selected according to differences in terms of pharmacodynamics (olanzapine having affinity for more receptors than risperidone). Because the pharmacokinetics of olanzapine is influenced by tobacco use (through cytochrome P450 1A2) patients' smoking habits (number of cigarettes smoked per day) were examined. Since it is difficult to recollect the baseline clinical and laboratory data of the subjects, we used disorder *versus* treatment time intervals such as:

- total duration of psychosis (DP) defined as the time interval (months) from the onset of the psychosis to present assessment;

- duration of pre-LAI treatment defined as the time interval (months) from the onset of the psychosis to the introduction of the LAI treatment;

- duration of LAI treatment defined as the time interval (months) of LAI treatment.

Because the disorder itself may increase the risk of developing metabolic syndrome through lifestyle and symptoms (depression, anxiety, elevated mood, motor hyperactivity, tension, excitement, self-neglect), the severity of the psychiatric symptoms was measured with BPRS-E (Brief Psychiatric Rating Scale, Expanded). This 24 item scale (12) is based on an earlier 16 item scale (BPRS) (13) and is useful as assessing scale in psychotic disorders (14). The correlation between BPRS and CGI-s (CGI: Clinical Global Impressions – severity) was done by Leucht and collaborators (15).

The following parameters were assessed:

socio-demographics (age, gender), clinical data (age at disorder onset, severity of psychiatric symptoms, time intervals related to disorder and treatment), laboratory data (fasting blood glucose, HDL cholesterol, triglyceride serum levels), blood pressure, waist circumference, smoking habits and psychotropic medication (antipsychotic and adjunctive mood stabilizers).

The new International Federation of Diabetes diagnostic criteria (2006) for MS were used (16):

- Central obesity (waist circumference with ethnicity specific values), plus any two of the following four factors:

- Raised triglycerides ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality;

- Reduced HDL cholesterol < 40 mg/dL (1.03 mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality;

- Raised blood pressure systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension;

- Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If above 5.6 mmol/L or 100 mg/dL, OGTT (oral glucose tolerance test) is strongly recommended but not necessary to define the presence of the syndrome.

Fasting blood glucose was measured using the PalmLab SC-101 glucometer. The lipid profile was determined using the LipidPro ILM-0001A lipid meter.

The study protocol and informed consent were approved by the Scientific Research Ethic Commission of “Victor Babes” Timisoara University of Medicine and Pharmacy. This project was conducted in accordance with the Helsinki Declaration. Each subject enrolled in the study signed a written informed consent. The authors have undertaken this study in the course of their employment, with no funding from any other source.

Statistical analysis

Version 20 of the IBM SPSS Statistics program was used to analyze data. Because of the non-gaussian data distribution (assessed with the Shapiro-Wilk test), to analyze group differences, non-parametrical tests (Mann-Whitney U) were applied. In order to check for associations between scores we used Spearman's correlation coefficients (for numerical data). For comparing categorical variables, the χ^2 (chi-square) test was utilized. The level of significance was set at 0.05 and all the results were two-tailed.

RESULTS

We analyzed 77 outpatients (41 on olanzapine LAI and 36 on risperidone LAI) diagnosed with schizophrenia and schizoaffective disorder, currently in remission (mean BPRS-E score of 38.38 ± 10.94 , which represents non-pathological symptom severity). The enrollment period was between 2015 and 2016. The socio-demographic and clinical characteristics of the entire sample are presented in Table 1.

The sample characteristics, according to the LAI antipsychotic dosages, are presented in Table 2.

We found that 58.4% of the studied subjects fulfilled the criteria for the MS. A study on Romanian population found a prevalence of 16.3% for the MS (using the IDF 2005 criteria) in a rural community (17). More than half of our patients presented dyslipidemia (hypertriglyceridemia and hypo-HDL cholesterol), which is in accordance with the results of another study on Romanian patients with schizophrenia that found an increased risk of dyslipidemia in these patients (18).

The metabolic syndrome and its components

Antipsychotics differ in their potential of inducing glucose and lipid metabolism dysfunctions in

respect to their pharmacodynamics. Molecules that have an antagonistic effect on hypothalamic histaminic 1 (H1) (19) and serotonergic 2c (5HT-2C) (20) receptors are orexigenic. Animal studies show that the H1 receptors blockade activates hypothalamic AMP-kinase in mice (21), and agonism on 5HT-2C receptors of the pro-opiomelanocortin neurons in the hypothalamus decreases food intake (22). Some antipsychotics antagonize muscarinic 3 (M3) receptors at the level of pancreatic β cells inhibiting the insulin secretion (23). Olanzapine is a multifunctional drug, thus combining antagonistic actions at H1, 5HT2C and M3 receptors that result in a strong impact on energy metabolism. After one year of treatment with olanzapine, blood glucose levels increase with an average of 10 mg/dL (24). Risperidone has a simpler pharmacologic profile (25) blocking H1 and α -adrenergic receptors and insignificantly the cholinergic receptors (26).

Antipsychotics also influence the lipid metabolism inducing hypertriglyceridemia, low HDL cholesterol and high LDL cholesterol serum levels. Treatment with clozapine and olanzapine was associated with the most important increase in total cholesterol, LDL cholesterol, and triglycerides and with decreased HDL cholesterol, while risperidone and quetiapine have

Table 1. Socio-demographic and clinical characteristics of the sample

Sample characteristics	Entire sample		Men		Women	
	n	%	n	%	n	%
	77		41	53.2	36	46.8
Mean age (years) at disorder onset	32.55		30.68		34.69	
	SD=12.45		SD=12.64		SD=12.04	
Mean age (years) at study entry	42.48		43.04		41.83	
	SD=11.34		SD=12.24		SD=10.35	
Psychiatric diagnostic						
Schizophrenia	59	76.6	31	52.5	28	47.5
Schizoaffective disorder	18	23.4	10	55.6	8	44.4
Mean BPRSE-E score	39.45		42.95		35.47	
	SD=13.26		SD=15.13		SD=9.46	
Mean BPRS-16 score	28.25		30.68		25.5	
	SD=9.38		SD=10.67		SD=6.79	
Associated mood stabilizer						
yes	49	63.6	25	51	24	49
no	28	36.4	16	57.1	12	42.9
Metabolic syndrome	45	58.4	26	57.8	19	42.2

Table 2. Sample characteristics according to LAI antipsychotic dosages

LAI Antipsychotic	Dosage (mg/months)	Number of patients n	Percentage %
Olanzapine	210	2	2.6
Olanzapine	300	9	11.7
Olanzapine	405	7	9.1
Olanzapine	2 x 300	23	29.9
Risperidone	2 x 37.5	14	18.2
Risperidone	2 x 50	22	28.5

intermediate effects on lipids (27).

We found no statistically significant differences between patients treated with olanzapine LAI and risperidone LAI regarding the presence of the MS. In a meta-analysis Mitchell and collaborators found that the rate of MS for olanzapine was 28.2% (95% CI = 19.1%–38.4%), and 27.9% (95% CI = 12.6%–46.5%) for risperidone using ATP III criteria (Adult Treatment Panel III of the National Cholesterol Education Program) (28). In a study conducted by Saddichha and collaborators, the maximum prevalence of MS was found in patients treated with olanzapine at 20–25% followed by risperidone at 9–24% (29). The differences in the prevalence of MS depend on the chosen criteria, 10.1% using ATP IIIA and 18.2% using IDF (29).

No differences between the two samples were found regarding the presence of hyperglycemia, hypertriglyceridemia, and hypo-HDL cholesterol.

Hypertension was found in significantly more patients treated with risperidone LAI than with olanzapine LAI ($\chi^2=4.383$, $p=0.036$). Also, subjects on risperidone had significantly higher values of both systolic ($Z=-2.716$, $p=0.007$) and diastolic ($Z=-2.517$, $p=0.012$) blood pressure. The patients presenting hypertension were significantly older than those without hypertension ($Z=-2.956$, $p=0.003$), but there were no differences between olanzapine and risperidone samples regarding the mean age at study entry. Other factors influencing blood pressure are the weight gain and disorder induced stress.

In respect to abdominal obesity, no differences between the two samples were found regarding the number of patients with high abdominal circumference. Nevertheless, subjects on risperidone LAI had significantly increased abdominal circumference ($Z=-2.191$, $p=0.028$) than those on olanzapine LAI. In the NIMH (National Institute of Mental Health)-funded CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) Schizophrenia Trial, Meyer and

collaborators found that at 3 months, olanzapine had the largest mean increase in waist circumference followed by risperidone (11).

In a multicenter, double-blind, randomized study with risperidone LAI, Kane and collaborators found small weight changes (0.5 kg, 1.2 kg, and 1.9 kg, respectively) in all risperidone groups (25-, 50-, and 75-mg) (30). In respect to olanzapine LAI, a literature review by Lindenmayer showed that significant weight gain is dose related (15.2%, 20.7%, 16.4% and 8.3%) for the following regimens: 300 mg every 2 weeks, 405 mg every 4 weeks, 150 mg every two weeks, 45 mg every 4 weeks. Significant increases in total cholesterol and fasting LDL cholesterol were found in the first three treatment regimens, with no significant differences regarding fasting triglyceride and glucose levels in-between the four olanzapine dose regimens (31). Using data from EUFEST, a naturalistic and randomized trial on antipsychotics in first episode schizophrenia, Matei *et al.* found treatment induced weight gain in the first three months, regardless of the type of antipsychotic (32).

The characteristics of olanzapine and risperidone samples are presented in Table 3.

The characteristics of olanzapine and risperidone samples according to the MS are illustrated in Table 4.

In order to discriminate between medication and disorder induced metabolic changes, we analyzed time intervals related to the total duration of the psychosis (DP), time to LAI treatment initiation (pre LAI treatment) and duration on LAI treatment.

Patients presenting MS had a longer DP ($Z=-2.215$, $p=0.027$) and longer duration of LAI treatment ($Z=-4.122$, $p<0.0001$) than those without MS, with no differences regarding the duration of pre-LAI treatment. This sustains the idea that MS may be the result of both the disorder and the antipsychotic treatment.

The subjects presenting abdominal obesity had longer DP ($Z=-2.461$, $p=0.014$), longer pre-LAI treatment period ($Z=-2.104$, $p=0.035$), and longer

Table 3. Olanzapine versus risperidone samples' characteristics

LAI antipsychotic		Entire sample		Olanzapine sample		Risperidone sample	
		n	%	n	%	n	%
Gender	males	77		41	53.2	36	46.8
	females	41	53.2	21	51.2	20	47.8
Mean age (years) at disorder onset		36	46.8	20	55.6	16	44.4
		32.55		32.41		32.72	
Mean age (years) at present assessment		SD=12.45		SD=11.83		SD=13.28	
		42.48		40.24		45.02	
Smokers		SD=11.34		SD=11.33		SD=10.94	
		33	42.9	16	48.5	17	51.5
Mean number of cigarettes/day		9.29		8.41		10.27	
		SD=12.94		SD=12.11		SD=13.93	

duration of LAI treatment ($Z=-2.719$, $p=0.007$) than those without abdominal obesity. This result may imply that abdominal obesity depends on the psychosis itself affecting life style, disorder induced stress, or antipsychotic treatment.

Glucose metabolism disturbances were not influenced by DP and the duration of pre LAI treatment had no influence on fasting glucose levels, but the duration of LAI treatment was significantly longer in patients with hyperglycemia ($Z=-2.239$, $p=0.025$).

Lipid metabolism disturbances such as hypertriglyceridemia and hypo-HDL cholesterol were not influenced by DP, the duration of pre-LAI treatment, or the duration of LAI treatment.

The subjects presenting hypertension ($Z=-2.306$, $p=0.021$) had longer DP and duration of pre LAI treatment ($Z=-2.309$, $p=0.021$), suggesting that hypertension might be influenced by the length of time spent on uncertain treatment (oral antipsychotic treatment or absence of treatment). We found positive correlations between total BPRS-E scores, and both the DP ($r=0.286$,

$p=0.012$) and the duration of pre-LAI treatment ($r=0.32$, $p=0.005$), while the duration of the LAI treatment did not influence the total BPRS-E score. This can imply that hypertension may be a consequence of the stress related to the psychosis reflected in higher BPRS-E scores in patients with a longer duration of psychosis and a longer pre LAI treatment period. When looking at BPRS-E sub-scores, symptoms such as hostility ($r=0.281$, $p=0.013$, $r=0.286$, $p=0.012$), grandiosity ($r=0.291$, $p=0.01$, $r=0.306$, $p=0.007$), unusual thought content ($r=0.252$, $p=0.027$, $r=0.287$, $p=0.011$), bizarre behavior ($r=0.305$, $p=0.007$, $r=0.315$, $p=0.005$), self-neglect ($r=0.251$, $p=0.028$, $r=0.259$, $p=0.023$), and tension ($r=0.227$, $p=0.048$, $r=0.258$, $p=0.024$) show statistically significant positive correlations with DP and pre LAI treatment period and no correlations with LAI treatment period. Items such as elevated mood ($r=0.261$, $p=0.022$), excitement ($r=0.235$, $p=0.039$), and distractibility ($r=0.241$, $p=0.035$), showed a positive correlation with pre LAI treatment period, and no correlations with DP and duration of LAI treatment.

Table 4. Olanzapine and risperidone sample characteristics according to the presence of the metabolic syndrome

LAI antipsychotic	Entire sample		Olanzapine		Risperidone	
	n	%	n	%	n	%
Metabolic syndrome	77		41	53.2	36	46.8
Central obesity (waist circumference men>94 cm, women>88 cm)	45	58.4	21	46.7	24	53.3
Raised triglycerides (>150 mg/dL)	57	74	28	49.1	29	50.9
Reduced HDL cholesterol (men< 40 mg/dL, women<50 mg/dL)	38	49.4	17	44.7	21	55.3
Raised blood pressure (BP >130/85 mmHg)	66	85.7	37	56	29	44
Raised fasting plasma glucose (FPG≥100 mg/dL)	29	37.7	11	38	18	62
	60	77.9	29	48.3	31	51.7

Table 5. The characteristics of patients who fulfilled the criteria for metabolic syndrome

Sample characteristics		Metabolic syndrome	
		n	%
		45	58.4
Gender	males	26	57.8
	females	19	42.2
Mean age (years) at disorder onset		30.11 ± 19.8	
Mean age (years) at present assessment		42.22 ± 10.25	
Duration of psychosis		165.11 ± 131.87	
Time interval to LAI initiation		140.51 ± 125.59	
Duration of LAI treatment		24.68 ± 18.9	
Number of cigarettes per day		10.22 ± 13.77	
BPRS-E total score		38.38 ± 10.94	
BPRS 16		27.71 ± 8.38	
LAI antipsychotic			
	olanzapine	21	46.7
	risperidone	24	53.3
Associated mood stabilizer		28	62.2
	carbamazepine (mean dose: 400 mg/day)	9	32.1
	sodium valproate (mean dose: 1000 mg/day)	16	57.1
	lamotrigininum (mean dose: 150 mg/day)	3	10.8

Patients on risperidone LAI presented higher BPRS-E sub-scores for somatic concern ($Z=-2.055$, $p=0.04$), than those on olanzapine. Subjects on olanzapine LAI had higher BPRS-E sub-scores for grandiosity ($Z=-2.58$, $p=0.01$), excitement ($Z=-2.143$, $p=0.032$), and motor hyperactivity ($Z=-2.422$, $p=0.015$).

Patients treated with risperidone LAI had a longer duration of LAI treatment ($Z=-3.282$, $p=0.001$) than those with olanzapine LAI. We found no differences between the two samples regarding DP, the duration of pre LAI treatment. This might explain why patients on risperidone LAI present higher values of abdominal circumference, than those on olanzapine LAI.

DISCUSSION

Adjunctive treatment

More than half of the patients with MS had an adjunctive mood stabilizer associated to the LAI antipsychotic (the type and dosage of these associated mood stabilizers are presented in Table 5). Nevertheless, we found no differences between subjects taking mood stabilizers and the presence of the MS.

Subjects with associated mood stabilizers had a significantly longer duration of pre LAI treatment ($Z=-2.055$, $p=0.04$). No differences were found between subjects with and without mood stabilizers regarding the DP and the duration of LAI treatment. We observed that the longer the DP and the pre LAI treatment period, the higher the BPRS-E scores. Patients taking mood stabilizers in association with antipsychotics had a similar DP but a longer duration of pre LAI treatment. This might be interpreted as a need to use polypharmacy in the evolution of the psychosis as inconstant treatment results in treatment resistance.

There were no differences concerning the mean age at study entry between patients with and those without mood stabilizers.

The characteristics of patients presenting the metabolic syndrome are illustrated in Table 5.

Smoking habits

We found no differences between smokers and non-smokers regarding the DP, the pre LAI treatment period, or the duration of LAI treatment. The same is true for the number of cigarettes smoked per day. Men smoked significantly more cigarettes per day than women ($Z=-2.761$, $p=0.006$). We found no differences between the two samples regarding the number of smokers and the number of cigarettes smoked per day. Smoking did not influence the abdominal circumference, blood

pressure, or the blood levels of glucose, triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol. Nicotine, as a metabolic inducer, may alter the blood levels of olanzapine but does not influence risperidone (33, 34). In this respect, and in the absence of olanzapine and risperidone blood levels measurements, one might inquire if tobacco use influences olanzapine concentrations. Literature data did not find any clear relationship between weight gain and the dose of antipsychotic (35, 36).

Age and gender

In our sample age and gender did not influence the presence of the MS or its components: abdominal obesity, hyperglycemia, hypertriglyceridemia, hypo-HDL cholesterol.

The DP ($Z=-2.193$, $p=0.028$) and the duration of pre-LAI treatment ($Z=-2.365$, $p=0.018$) was significantly longer in men than in women.

There were no differences regarding the age at disorder onset or the age upon study entry between men and women, between the two LAI treatment samples, or between patients with and without associated mood stabilizers.

The presence of the metabolic syndrome, high glucose blood levels, triglycerides and low levels of HDL cholesterol were not influenced by the type of the antipsychotic or by the associated mood stabilizer. Treatment with risperidone was associated with higher rates and values of hypertension and higher values of abdominal circumference.

In conclusion, the development of the metabolic syndrome and abdominal obesity may be the consequence of both the antipsychotic treatment and the disorder itself. Hyperglycemia appears to be linked more with the antipsychotic treatment, while hypertension is possibly favored by age and the stress correlated with the psychosis.

The fact that total BPRS-E scores showed positive correlations with the total duration of the psychosis and the duration of pre-LAI treatment, but not with the duration of the LAI treatment, possibly implies that although untreated or insufficiently treated psychosis may result in residual symptoms, one might expect a clinical benefit of the LAI treatment in preventing worsening of psychosis and treatment resistance.

The strength of our study relies on the fact that parameters were measured in patients using long acting antipsychotics which ensures, in addition to a controlled treatment adherence, lower and constant serum concentrations of antipsychotic medication. Also,

it is a double-centered, observational study conducted on subjects in an outpatient care environment. Nevertheless, in a real-life setting, it is difficult to ensure baseline data collection, as in randomized-controlled studies.

Conflict of interest

The authors declare that they have no conflict of interest.

Limitations

As study limitations, we did not assess other risk factors for obesity such as physical inactivity, unhealthy diet, family history of obesity, thyroid hormone levels.

References

- Gilmer TP, Dolder CR, Lacro JP, Folsom DP, Lindamer L, Garcia P, Jeste DV. Adherence to treatment with antipsychotic medication and health care costs among Medicaid beneficiaries with schizophrenia. *Am J Psychiatry* 2004; 161(4):692-699.
- Bridler R, Umbricht D. Atypical antipsychotic in treatment of schizophrenia. *Swiss Med Wkly* 2003; 133:63-73.
- Hanley AJ, Karter AJ, Williams K, Festa A, D'Agostino Jr RB, Wagenknecht LE, Haffner SM. Prediction of type 2 diabetes mellitus with alternative definitions of the metabolic syndrome: the Insulin Resistance Atherosclerosis Study. *Circulation* 2005; 112:3713-3721.
- Gami AS, Witt BJ, Howard DE, Erwin PJ, Gami LA, Somers VK, Montori VM. Metabolic syndrome and risk of incidence cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol* 2007; 49:403-414.
- Zipursky RB, Gu H, Green AI, Perkins DO, Tohen MF, McEvoy JP, Strakowski SM, Sharma T, Kahn RS, Gur RE, Tollefson GD, Lieberman JA. Course and predictors of weight gain in people with first episode psychosis treated with olanzapine or haloperidol. *Br J Psychiatry* 2005; 187:537-543.
- Kohen D. Diabetes mellitus and schizophrenia: historical perspective. *Br J Psychiatry* 2004; 184(47):164-166.
- Remington G. Schizophrenia, Antipsychotics, and the Metabolic Syndrome: Is There a Silver Lining? *Am. J. Psychiatry* 2006; 163:1132-1134.
- Bushe C, Holt R. Prevalence of diabetes and impaired glucose tolerance with schizophrenia. *Br J Psychiatry* 2004; 184:67-71.
- Alison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001; 62(7):22-31.
- Davidson S, Judd F, Jolley D, Hocking B, Thompson S, Hyland B. Cardiovascular risk factors for people with mental illness. *Aust NZ J Psychiatry* 2001; 35(2):196-202.
- Meyer JM, Davis VG, Goff DC, McEvoy JP, Nasrallah HA, Davis SM, Rosenheck RA, Daumit GL, Hsiao J, Swartz MS, Stroup TS. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. *Schizophr Res* 2008; 101(1):273-286.
- Lukoff D, Nuechterlein KH, Ventura J. Manual for the Expanded BPRS. *Schizophr Bull* 1986; 12:584-602.
- Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962; 10:790-812.
- Velligan D, Prihoda T, Dennehy E, Biggs M, Shores-Wilson K, Crismon ML, Rush AJ, Miller A, Suppes T, Trivedi M, Kashner TM, Witte B, Toprac M, Carmody T, Chiles J, Shon S. Brief psychiatric rating scale expanded version: How do new items affect factor structure? *Psychiatry Res* 2005; 135(3):217-228.
- Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel R. Clinical Implications of Brief Psychiatric Rating Scale scores. *Br J Psychiatry* 2005; 187:366-371.
- Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome - a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetic Medicine* 2006; 23:469-480.
- Mihalache L, Graur LI, Popescu DS, Boiculescu L, Badiu C, Graur M. The prevalence of the metabolic syndrome and its components in a rural community. *Acta Endo (Buc)* 2012; 8(4):595-606.
- Ladea M, Exergian AM, Barbu CM. Dyslipidemia in psychiatric patients with schizophrenia, treated with antipsychotics. *Acta Endo (Buc)* 2013; 9 (4):647-653.
- Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, Roth BL. H1-histamine receptor affinity predicts short term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacol* 2003; 28:519-526.
- Reynolds GP, Hill MJ, Kirk SL. The 5-HT2C receptor and antipsychotic-induced weight gain—mechanisms and genetics. *J Psychopharmacol* 2006; 20(4):15-18.
- Kim SF, Huang AS, Snowman AM, Teuscher C, Snyder SH. Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. *Proc Natl Acad Sci USA* 2007; 104:3456-3459.
- Lencz T, Robinson DG, Napolitano B, Sevy S, Kane JM, Goldman D, Malhotra AK. DRD2 promoter region variation predicts antipsychotic-induced weight gain in first episode schizophrenia. *Pharmacogenet Genomics* 2010; 20(9):569-572.
- Robinson DS. Insulin secretion and psychotropic drugs. *Prim Psychiatry* 2006; 13:26-27.
- Meyer JM. A retrospective comparison of lipid, glucose and weight changes at one year between olanzapine and risperidone treated inpatients. *J Clin Psychiatry* 2002; 63:425-433.
- Stahl SM. *Essential Psychopharmacology, Neuroscientific Basis and Practical Applications*, Second Edition, Cambridge University Press, 2000: 433.
- Megens AAHP, Awouters FHL, Schotte A, Meert TF, Dugovic C, Niemegeers CJE, Leysen JE. Survey on the pharmacodynamics of the new antipsychotic risperidone. *Psychopharmacology* 1994; 114(1):9-23.
- American Diabetes Association. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes care* 2004; 27(2):596-601.
- Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders - a systematic review and meta-analysis. *Schizophrenia bulletin* 2013; 39(2):306-18.
- Saddichha S, Manjunatha N, Ameen S, Akhtar S. Metabolic syndrome in first episode schizophrenia - a randomized double-blind controlled, short-term prospective study. *Schizophr Res* 2008; 101(1):266-272.
- Kane JM, Eerdekens M, Lindenmayer JP, Keith SJ, Lesem M, Karcher K. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 2003; 160(6):1125-1132.
- Lindenmayer JP. Long-acting injectable antipsychotics: focus on olanzapine pamoate. *Neuropsychiatr Dis Treat* 2010; 6(6):261-267.
- Matci VP, Mihailescu A, Paraschiv G, Al-Bataineh R, Purnichi T. Weight gain and antipsychotics. Data from EUFEST study. *Acta Endo (Buc)* 2016; 12(2):177.
- Carrillo JA, Herráiz AG, Ramos SI, Gervasini G, Vizcaíno S, Benítez J. Role of the smoking-induced cytochrome P450 (CYP) 1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine. *J Clin Psychopharmacol* 2003; 23(2):119-127.
- Gex-Fabry M, Balant-Gorgia AE, Balant LP. Therapeutic drug monitoring of olanzapine: the combined effect of age, gender, smoking, and comedication. *Ther Drug Monit* 2003; 25(1):46-53.
- Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects. *CNS drugs* 2005; 19(1):1-93.
- Simon V, van Winkel R, De Hert M. Atypical Antipsychotics Dose Dependent? A Literature Review. *J Clin Psychiatry* 2009; 70(7):1041-1050.