R E V I E W

Etiology of cardiovascular disease in patients with schizophrenia: current perspectives

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Abstract: Cardiovascular morbidity and mortality are important problems among patients with schizophrenia. A wide spectrum of reasons, ranging from genes to the environment, are held responsible for causing the cardiovascular risk factors that may lead to shortening the life expectancy of patients with schizophrenia. Here, we have summarized the etiologic issues related with the cardiovascular risk factors in schizophrenia. First, we focused on heritable factors associated with cardiovascular disease and schizophrenia by mentioning studies about genetics–epigenetics, in the first-episode or drug-naïve patients. In this context, the association and candidate gene studies about metabolic disturbances in schizophrenia are reviewed, and the lack of the effects of epigenetic/posttranscriptional factors such as microRNAs is mentioned. Increased rates of type 2 diabetes mellitus and disrupted metabolic parameters in schizophrenia are forcing clinicians to struggle with metabolic syndrome parameters and related issues, which are also the underlying causes for the risk of having cardiometabolic and cardiovascular etiology. Second, we summarized the findings of metabolic syndrome-related entities and discussed the influence of the illness itself, antipsychotic drug treatment, and the possible disadvantageous lifestyle on the occurrence of metabolic syndrome (MetS) or diabetes mellitus. Third, we emphasized on the risk factors of sudden cardiac death in patients with schizophrenia. We reviewed the findings on the arrhythmias such as QT prolongation, which is a risk factor for Torsade de Pointes and sudden cardiac death or P-wave prolongation that is a risk factor for atrial fibrillation. For example, the use of antipsychotics is an important reason for the prolongation of QT and some other cardiac autonomic dysfunctions. Additionally, we discussed relatively rare issues such as myocarditis and cardiomyopathy, which are important for prognosis in schizophrenia that may have originated from the use of antipsychotic medication. In conclusion, we considered that the studies and awareness about physical needs of patients with schizophrenia are increasing. It seems logical to increase cooperation and shared care between the different health care professionals to screen and treat cardiovascular disease (CVD)-risk factors, MetS, and diabetes in patients with psychiatric disorders, because some risk factors of MetS or CVD are avoidable or at least modifiable to decrease high mortality in schizophrenia. We suggested that future research should focus on conducting an integrated system of studies based on a holistic biopsychosocial evaluation.

Keywords: antipsychotic, cardiovascular risk, MetS, miRNA, QTc, schizophrenia

Introduction

Cardiovascular death is a major contributor to the increased mortality rate (two- to threefold) and to the decreased life expectancy of 20% in schizophrenia victims according to normal population.[1–3] The causes for increasing the mortality rate in schizophrenia victims are mostly similar to those in the general population with metabolic syndrome and diabetes mellitus. In addition, some disease-specific risk factors may also contribute to the increasing mortality rate such as follows: being genetically liable or having overlapping genes between cardiovascular disease, sudden cardiac

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death and schizophrenia. Requiring antipsychotic drugs and outcomes of such drugs, lifestyle due to negative symptoms, smoking, and alcohol abuse, and inability to obtain good medical care or inability to reach qualitative medical opportunities might also add some risks. In this review, we conducted a retrospective database study to assess the primary potential risk factors of cardiac mortality in first-episode and chronic patients with schizophrenia in light of recent findings in the literature.

Methods

We conducted a systematic search for potentially relevant articles published between the year 1995 and 2015. Our search strategy was to assess the studies in earlier stages of schizophrenia including first-episode psychosis/schizophrenia, first-degree relatives, schizophrenia and cardiac mortality (single nucleotide polymporhisms or microRNA (miRNA) or modifiable risk factors or sudden death or QTc, or P-wave, Torsade de Pointes [TdP]), and glucose or insulin or cholesterol or triglycerides, or blood pressure or weight using health-related databases such as MEDLINE (via PubMed), Embase, and PsycINFO. We have focused on risk factors for mortality and we included systematic reviews, meta-analyses, and studies. We did not attempt to identify unpublished work or search in non-English- written journals.

Findings about genetic and epigenetic mechanisms

The increase in cardiovascular risk factors has also been revealed in antipsychotic naïve first-episode patients,[4] before antipsychotic drug invention in the 1920s[5] and even in their healthy relatives.[6] Thus, one may consider whether some common candidate genes are present or not between schizophrenia and cardiovascular risk-prone victims (Table 1).

Atypical antipsychotic-related weight gain was revealed to be associated with *INSIG2*,[7] or the interaction of INSIG2 with *INSIG1*.[8] The same investigators detected a significant association between rs498177 single nucleotide polymorphism (SNP) in the serotonin 5-HT2C receptor gene and metabolic syndrome only in female patients with schizophrenia.[9] An association was shown between the endothelial nitric oxide synthetase (eNOS) T-786C genetic variant and endothelial functioning, which was no longer detectable if patients met the criteria of metabolic syndrome.[10]

Besides possible cardiovascular outcomes, in a genome-wide association study (GWAS), common SNPs in the cardiomyopathy-associated gene (*CMYA5*) were also accused for

Table 1 Genetics in cardiometabolic risk factors in schizophrenia

Authors	Participants	Design	Results
Hansen et al[6]	420 Danish patients with schizophrenia, two healthy controls for each patient	Type 2 diabetes mellitus-risk-related single nucleotide polymorphism	At-risk allele in TCF7L2 (rs79031146) was associated with schizophrenia
Le Hellard et al[7]	160 first-time users of clozapine with a mean dose was 285±121 mg/day in schizophrenia patients	All were monitored for the changes in body mass index during clozapine treatment	Strong association between weight gain and rs17587100, rs10490624, and rs17047764, localized in/near *INSIG2* gene
Liou et al[8]	456 schizophrenia patients with an average treatment of 45.5±27.6 months; with clozapine (n=171), olanzapine (n=91), risperidone (n=194)	The association of SNPs in *INSIG1* and *INSIG2* in MetS or without MetS. The gene–gene interaction model of *INSIG1* and *INSIG2*	The INSIG2 rs11123469-C homozygous genotype was more frequent in patients with MetS. Interactions between *INSIG1* and *INSIG2* were significant
Bai et al[9]	456 schizophrenia inpatients; clozapine (n=171), olanzapine (n=91, risperidone (n=194)	6 tag SNPs, capturing all common genetic variations in the *HTR2C* gene	The rs498177 SNP showed a significant association with MetS in female patients
Burghardt et al[10]	203 patients under-treatment with schizophrenia or schizoaffective disorder	eNOS genetic variants and endothelial function (artery tonometry) were assessed	Association between eNOS T-786C and worse endothelial functioning only in patients without MetS

Note: Data are presented as mean ± standard deviation.
Abbreviations: SNP, single nucleotide polymorphism; eNOS, endothelial nitric oxide synthetase; MetS, metabolic syndrome.

schizophrenia.[11] Some authors have revealed an association between rs10503929 within the *NRG1* gene and sudden unexpected deaths due to ventricular fibrillation in schizophrenia victims.[12–14] In a five-drug-specific GWAS, genome-wide significance was detected with SNP rs4959235 at *SLC22A23* which mediated the effects of quetiapine on QTc prolongation in patients from the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) study (Table 2).[15]

miRNAs are small noncoding RNAs that bind to the 30-UTR (untranslated region) of usually many messenger RNAs. Through multiple mechanisms affecting transcription and translation, miRNAs are among the key regulators of posttranscriptional gene expression.[16] In a systematic review, different alterations among miRNA were reported in the postmortem brains of schizophrenia patients.[17] Perkins et al have investigated alterations of miRNAs in 179 rats treated with haloperidol and detected increments of miR-199a, miR-128a, and miR-128b.[18] On the contrary, the downregulation of miR-31 and miR-342-5p was shown in peripheral blood mononuclear cells in vivo in schizophrenia patients.[19] In a recent study, for the first time, the alteration of miRNAs after olanzapine has been found to be associated with metabolic pathway via pathway analysis in mice.[20]

Findings on cardiometabolic risk factors

Data from the general population estimated five metabolic risk factors for predisposition to cardiovascular disease (CVD) approximately twofold increase[21] and to diabetes approximately three- to fourfold increase[8,22] and widely shaped as: abdominal obesity, elevated triglycerides, reduced high density lipoprotein (HDL) cholesterol, high blood pressure, and elevated fasting blood glucose levels.

In a systematic review of 25 studies in which the average follow-up duration was 31.7 weeks (from January 1990 to June 15, 2010), no difference in metabolic syndrome (MetS) was detected in drug-naïve patients than healthy controls.[1] On the contrary, some authors had found a higher waist/hip ratio[23,24] and more visceral fat[25] in first-episode patients with schizophrenia than controls although inadequate control matching was an important limitation of these studies. The European First Episode Schizophrenia Trial (EUFEST) was a 1-year open label study in which first-episode (<2 years) or partially antipsychotic naïve patients were recruited. Partially antipsychotic naïve was defined as the use of any antipsychotic drug <2 weeks in the previous year or <6 week antipsychotic treatment at any time including haloperidol, amisulpride, ziprasidone, quetiapine and olanzapine. In that study, the baseline rate of MetS was similar in the drug-naïve and brief antipsychotic use groups and in the general population in Europe (Table 3). Interestingly, 58.5% of the patients have shown individual risk factors for one or more elevated metabolic risks at the baseline as following: 28.5% suboptimal HDL, 24.2% hypertension, 17.7% hyper-triglyceridemia, 8.2% abdominal obesity, and 7.3% hyperglycemia.[28] A meta-analysis was performed with 126 valid analyses from 77 published studies (n=25,692) and data from 14 of these 77 studies (n=800) were included for analysis which had examined first-episode psychosis and/or

Table 2 Genetics in cardioautonomic risk factors

Authors	Participants	Design	Results
Chen et al[11]	25 samples with a total of 33,834 subjects, including 912 families with 4,160 subjects, 13,038 cases and 16,636 controls	GWA analyses study in the *CMYA5* gene	rs10043986 and rs4704591 were significantly associated with schizophrenia
Nicodemus et al[12]	296 schizophrenia, 365 healthy controls and a separate sample of controls for neuroimaging (n=172)	Association between SNPs and the relationship between SNPs and BOLD during the working memory by fMRI	Interaction between *NRG1* 5′ and rs4560751–rs3802160 and schizophrenia, validated using fMRI of working memory
Huertas-Vazquez et al[14]	Oregon study, 340 SCD cases presenting with ventricular fibrillation and 342 controls	17 SNPs mapped to 14 loci related with schizophrenia and epilepsy was tested	SNP rs10503929 within the *NRG1* gene was associated with SCD
Aberg et al[15]	492,000 SNP genotypes from 738 schizophrenia patients from the CATIE study	Antipsychotic-induced QTc prolongation; a GWA study	Association of rs4959235 and quetiapine/QTc within gene *SLC22A23*
Santarelli et al[20]	miRNA profile in mice treated with haloperidol (n=11), olanzapine (n=11) or clozapine (n=12) for 7 days and saline group (n=11)	45 total mouse whole brain RNA samples were used for microarray profiling	Down regulation of miR-193, miR-223, miR-544 in DLPC by olanzapine; upregulation of miRNA-339 in BA22 in haloperidol

Abbreviations: GWA, genome-wide association; SNP, single nucleotide polymorphism; RNA, ribonucleic acid; miRNA, microRNA; QTc, heart rate-corrected QT interval; CATIE, Clinical Antipsychotic Trial of Intervention Effectiveness; fMRI, functional magnetic resonance imaging; SCD, sudden cardiac death; DLPFC, dorsolateral prefrontal cortex; BOLD, blood oxygen level-dependent.

Table 3 Cardiometabolic risk factors in first-episode psychosis

Authors	Participants	Design	Results
Foley et al[1]	Drug naïve or with a short-time drug treatment, sample size varied (n=9–555)	Review of 25 longitudinal studies and of which 8 have controls	No difference in cardiometabolic indices; risk increases after first exposure to any antipsychotics
Correll et al[2]	Patients in FES programs, had less than 6 months of antipsychotic treatment	Baseline findings in the RAISE study	13.2% of FES patients met the criteria of MetS
Saddichha et al[23]	66 FEP patients initiating to olanzapine, haloperidol, or risperidone	Randomized, case-control and a prospective study (for a period of 6 weeks)	Baseline obesity prevalence was 30 times higher in patients; olanzapine, 5.1 kg > risperidone, 4.1 kg > haloperidol, 2.8 kg
Ryan et al[25]	19 drug naïve, FEP patients, and 19 matched controls, started to receive olanzapine or risperidone	Fatness and fat distribution parameters were measured	Baseline intra-abdominal fat was significantly higher in patients; no significant increase in intra-abdominal fat distribution after atypicals
Fleischhacker et al[26]	498 patients with FEP, EUFEST study; visits at the 13th, 26th, 39th and 52nd weeks	1-year open label study including baseline MetS indices	Baseline MetS prevalence was 5.7% in drug-naïve and 6.1% in briefly antipsychotics exposed patients

Abbreviations: FES, first-episode schizophrenia; FEP, first-episode psychosis; EUFEST, European First Episode Schizophrenia Trial; MetS, metabolic syndrome; RAISE, Recovery After an Initial Schizophrenia Episode.

drug-naïve patients. Although no comparison with general population was detected within all these 14 studies, the MetS rate was established to be 11.3% (95% CI =7.3%–16.1%)[27] that was surprisingly lower, while the estimated prevalence of the MetS rate in Europe was 18%–20%[28] and 25% in the general population in the USA.[29]

It is commonly accepted that the prevalence of MetS in patients with chronic schizophrenia is higher than that in the normal population. In the CATIE study, the rate of MetS in schizophrenia was found to be 40.9% vs 23.7% in controls (for males 36.0% vs 19.7%; for females 51.6% vs 25.1%).[30] In the aforementioned meta-analysis (126 analyses from 77 published studies, n=25,692), the overall rate of MetS was 32.5% (34.8% in males and 34.8% in females). Additionally, MetS was present in 39.2% of older patients with a mean age of 50 years or above[27] which shows that the MetS rate is rising with aging in patients with schizophrenia (Table 4).

The overall findings according to this meta-analysis were as follows: the rate of being overweight was 49.4% (N=53) and 44.4% (N=8) according to two different criteria of waist circumference measurement. Hyperglycemia was detected in 19.5% of patients (N=147, n=13,784), while increased triglyceride was 39.3% (N=77, n=19,831), decreased HDL was 42.6% (N=76, n=19,280), high blood pressure was 38.7% (N=72, n=18,657), and presence of diabetes was 10.9% (N=14, n=2,186).[27] In addition, the rate of diabetes was reported as being 16% in females and 11% in males with schizophrenia, and only 3% in controls,[31] or reported to be 2.5–3-fold higher in the 1990s even before the extensive presence of atypical antipsychotics on the counter.[32]

In the EUFEST study, the patients had a significantly greater weight gain and increased waist circumference in amisulpride and haloperidol groups than the ziprasidone group at weeks 26, 39, and 52, while no significant change

Table 4 Cardiometabolic risk factors in patients with chronic schizophrenia

Authors	Participants	Design	Results
McEvoy et al[30]	n=689 chronic patients with schizophrenia	CATIE, a national, multisite, prospective trial of anti-psychotic effectiveness	Baseline MetS was 40.9%–42.7% in patients, 23.7% in normal subjects
Goff et al[31]	n=689 chronic patients with schizophrenia	CATIE	The presence of diabetes was 13% and 3% in normal subjects
Dixon et al[32]	Large population under treatment for schizophrenia (n=20,248)	The schizophrenia Patient Outcomes Research Team study	The rate of diabetes was found to be 2.5–3-fold higher than general population
Arranz et al[35]	Patients with schizophrenia; standard olanzapine tablets (n=19), and disintegrating olanzapine (n=19)	Prospective study (6 weeks)	Significant increase in weight 6.3±1.9 kg vs 3.3±3.2 kg and in BMI 2.1 kg/m² vs 1.1 kg/m² in standard than disintegrating olanzapine
Hägg et al[37]	269 under-treatment patients with schizophrenia	A cross-sectional Northern Sweden study	MetS was 34.6% and the highest in clozapine-treated patients, ie, 48%

Note: Data are presented as mean ± standard deviation.
Abbreviations: CATIE, clinical antipsychotic trial of intervention effectiveness; MetS, metabolic syndrome; BMI, body mass index.

was detected with respect to weight gain between groups at the first visit. Besides, weight gain and waist circumference were significantly higher at each time-point in the olanzapine and quetiapine groups than in the ziprasidone group.[26] In this study, no significant changes were seen between antipsychotic trial groups with respect to the blood levels of glucose, total cholesterol, triglyceride, and HDL. However, in a systematic review of FEP trials, the influences of antipsychotic drugs were tested in 25 studies in which the average follow-up time across was 31.7 weeks (ranged from 4 weeks to 2.5 years). Significant changes were common at the sixth month with regard to the total body weight, HDL, low density lipoprotein (LDL), triglycerides, fasting glucose and insulin levels.[1] In this review, the weight gain in olanzapine (5–6 kg) was significantly higher than risperidone (4 kg), and haloperidol (3 kg) at weeks 6–8, while the difference between olanzapine and risperidone was waned at weeks 12–16 (7–9 kg vs 6 kg, respectively).[1] The weight gain did not differ for 1 year across olanzapine, risperidone, clozapine, amisulpride, quetiapine fumarate, and haloperidol.[1] Interestingly, a question was raised as to whether orally disintegrating tablets may have lesser effects on weight gain or not than standard tablets (Table 4).[35] Although the number of hyperglycemia cases had increased after 52 weeks in the first episode of the psychosis Comparison of Atypicals in First Episode of Psychosis (CAFÉ) study[36] and small amounts of increases in the blood glucose level was noted in the EUFEST[28] study groups, no difference was informed between various first- and second-generation antipsychotics. Risperidone was related to the smallest elevations of the triglyceride level in fasting and the smallest reduction in the HDL level than the other comparators such as olanzapine and quetiapine in the CAFÉ study.[36]

The pathophysiology of the underlying MetS is not clear due to antipsychotic use, and an increased risk of CVD cannot be exactly attributed to antipsychotics or socio-demographical aspects of patients with schizophrenia.[34] In a Sweden study, the MetS rate was higher in chronic patients treated with clozapine.[39] In CATIE study (n=689), at the time of assessment, the groups were as follows: 24.8% were drug free/-naïve, 58.4% were taking an atypical antipsychotic, 11.9% were under conventional antipsychotic treatment, and 5.0% were taking a combination of antipsychotics. It was found that diabetes mellitus and hypertension and a significantly lower HDL level was significantly more frequent in patients with schizophrenia than that in controls.[33] In the seminal meta-analysis of Mitchell et al (N=112 studies and n=24,892 patients), 35.3% frequency of MetS in all schizophrenia patients and a 39.2% frequency of MetS in older patients (N=14, n=6,396) have been reported.[27] According to this meta-analysis, using Adult Treatment Panel III criteria, only three drug monotherapy comparisons were possible: the MetS rate was 51.9% (N=13, n=673) for clozapine; 28.2% (N=12, n=1,056) for olanzapine; and 27.9% (N=9, n=659) for risperidone. However, the finding of clozapine in this meta-analysis might have confounders as old age and a longer duration of illness.[27]

Findings on cardiomyopathic risk factors and sudden cardiac death

In 1899, Emil Kraepelin mentioned extensive autonomic alterations in patients with schizophrenia, such as increased heart rates, altered pupillary function, increased sweating and salivation, and body temperature changes; these described signs suggest increased sympathetic output, decreased para-sympathetic modulation, or both.[38]

Table 5 Cardiomyopathic risk factors in first-episode schizophrenia or at risk populations

Authors	Participants	Design	Results
Emul et al[39]	Schizophrenia inpatients (n=11), drug free (<4 weeks), 11 controls	ECG reports prior to ziprasidone and 1.5–2 h after an IM injection	Baseline P-wave dispersion was significantly longer in patients; no changes after ziprasidone IM have detected among ECG variables
Toichi et al[40]	53 chronic patients (n=22 acute psychotic attack, n=31, stable), 53 healthy controls	In ECG, cardiac autonomic functions were based on heartbeat intervals	In psychotic attack, parasympathetic index was significantly decreased without significant changes in the sympathetic index
Bär et al[41]	Paranoid schizophrenia (n=36), 36 first-degree relatives, controls (n=36)	Cross-sectional, case-control study	Evidence for reduced HRV as well as augmented QT variability in first-degree relatives
Jindal et al[42]	24 neuroleptic-naïve FEP patients, 26 controls	ECG data were collected between 8 and 10 am	Significantly increased QTV and decreased RRV. No correlation between psychotic symptom severity and HRV abnormalities
Zhao et al[48]	27 FEP, the initiation of oral ziprasidone (up to 120–160 mg/day)	Prospective, 8 weeks; 16 dropped out; data of 11 patients were analyzed	The mean QT prolongation was 20 ms, no QTc prolongation >500 ms

Abbreviations: ECG, electrocardiogram; RRV, RR interval variability; QTc, heart beat-corrected QT interval; FEP, first-episode psychosis; h, hour; IM, intramuscular; HRV, heart rate variability; QTV, QT interval variability; QT, QT interval.

In the last 2 decades, the compromised autonomic system in schizophrenia patients[38–40] and in first-degree relatives of patients with schizophrenia[43] has been accused for a number of cardiac abnormalities (Table 5). Autonomic dysfunction is most likely the consequence of long-lasting stressful experiences associated with the psychotic state, in addition to a genetic underlying predisposition to autonomic dysfunction as observed in the relatives of patients.[38] For example, decreased RR interval variability (RRV), which is a marker for cardiac parasympathetic activity, has been reported to predict potential fatal ventricular tachycardia.[42] Depression with psychotic features in a Finnish study[43] has also been suggested as a risk factor for sudden death and other arrhythmic events.[44] Jindal et al concluded that drug-naïve patients with first-episode psychosis may have an impaired cardiac autonomic function.[42]

In a meta-analysis study, antipsychotics were reported to increase risk by two- to sixfold for ventricular arrhythmias, sudden cardiac death, and lengthening of heart rate-corrected QT interval (QTc), and it has been widely accepted as a marker of predicting drug-associated cardiac events[45] although no clear evidence for the QT interval prolongation (>500 ms) is related with increased risk for TdP – an increased risk of ventricular tachyarrhythmia – or sudden cardiac death.[44,46] Some questions rise whether there is any difference between atypical and typical antipsychotic drugs in the literature.[47] In a recently published study, no meaningful changes after ziprasidone use was detected in 27 first-episode psychosis (illness duration of <3 years, previous antipsychotic exposure lasting for <2 consecutive weeks).[48]

Indeed, the prolonged QT interval was detected in 8%–23% of patients under antipsychotics treatment and in 2% of healthy controls, while a dose-dependent correlation between the risk of QT lengthening effects and antipsychotic use has also been emphasized.[49,50]

In a meta-analysis study of seven atypicals (aripiprazole, amisulpride, sertindole, risperidone, quetiapine, olanzapine, and ziprasidone), the authors have collected data of 16 randomized controlled trials (RCTs) from 42 RCTs.[45] They have found that aripiprazole was the only atypical drug that shows both significantly smaller mean change in QTc ($P=0.03$) and significantly lower risk to cause QTc prolongation ($P=0.04$), while sertindole was informed with a significant QTc prolongation ($P<0.0001$).[45] In another study, the QTc interval prolongation effects were ranked as: thioridazine $>$ ziprasidone $>$ quetiapine $>$ risperidone $>$ olanzapine $>$ haloperidol.[52] One of the main questions was sex differences, because it is well-known that females are more prone to QT prolongation as found in a study that the mean QTc interval was shorter in males (391 ± 31 ms vs 400 ± 37 ms, $P<0.001$).[52] In a recent study according to the mean QTc interval, the results were as follows: quetiapine = olanzapine but quetiapine $>$ risperidone and aripiprazole, and olanzapine $>$ risperidone (Table 6). However, in this study,

Table 6 Cardiomyopathic risk factors in chronic schizophrenia and use of antipsychotic drugs

Authors	Participants	Design	Results
Harrigan et al[51]	Haloperidol (n=27) 15 mg/day; thioridazine (n=30) 300 mg/day; ziprasidone (n=31) 160 mg/day; quetiapine (n=27) 750 mg/day; olanzapine (n=24) 20 mg/day, or risperidone 6–8 mg/day increased to 16 mg/day (n=25/20)	Psychotic patients, open-label, randomized, parallel-group, the influences of 6 antipsychotics on QTc	None of drugs >500 ms on QTc; the mean QTc increments: in thioridazine (30.1 ms), in olanzapine (1.7 ms), in ziprasidone (15.9 ms), in haloperidol (7.1 ms), in quetiapine it was (5.7 ms) and in risperidone groups (3.9 ms and 3.6 ms)
Yang et al[52]	Under-treatment inpatients schizophrenia (n=1,006) (male, 689 and female, 317) and age- and sex-matched controls (n=456)	Naturalistic	Prolonged QTc was 4.5%; (3.2% in males and 7.3% in females); QTc in clozapine was significantly longer than risperidone and typicals; QTc in risperidone = typical
Suzuki et al[53]	Schizophrenia (n=222) with OLZ (n=69), RIS (n=60), ARP (n=62), or QTP (n=31)	QTc interval in chronic schizophrenic patients	QTP $>$ RIS ($P=0.002$) QTP $>$ ARP ($P=0.029$) OLZ $>$ RIS ($P=0.006$)
Hasnain et al[56]	Amisulpride (n=83); clozapine (n=73); quetiapine mono/combined (n=286); risperidone (n=45), ziprasidone (n=56)	Overdoses of different antipsychotics on QTc and TdP	Amisulpride, 7%, TdP; clozapine, 8.2% QTc prolongation; quetiapine, 8.4% borderline QTc; risperidone, 58% tachycardia ziprasidone, 2% TdP and 12.5% borderline QTc prolongation
Suzuki et al[57]	25 schizophrenia outpatients	Follow-up study after olanzapine use	Significant increase in PR interval, not more than 200 ms; no significance in the QT interval
Bayar et al[59]	15 schizophrenia receiving antipsychotics, 15 controls	ECG records at baseline and after the 3rd ECT	Baseline P minimum duration was shorter in patients; significant increase in P maximum duration after the 3rd ECT; no changes after the 3rd ECT in P-wave dispersion, QTc, and QT dispersion

Abbreviations: OLZ, olanzapine; RIS, risperidone; QTP, quetiapine QT interval; ECG, electrocardiogram; QTc, heart beat-corrected QT interval; TdP, Torsade de Pointes; ECT, electroconvulsive therapy; ms, milliseconds; ARP, aripiprazole; QT, QT interval.

the mean chlorpromazine equivalent doses of olanzapine and quetiapine were significantly higher than risperidone and aripiprazole groups. In this study, the average QTc in females was significantly longer only in the olanzapine group.[53] However, in a few studies, no sex difference in QTc was demonstrated in various antipsychotic use such as depot, atypical, or typicals.[49,54,55]

Although there are extensive studies on QTc, very few studies have emphasized on the PR interval in the literature.[39,57] In fact, prolongation of the PR interval might lead to atrial fibrillation, pacemaker indication, and mortality.[58] Emul et al have not found a difference on PR after intramuscular ziprasidone administration[39] while a significantly increased PR interval after the third electroconvulsive therapy (ECT) session was reported in patients with schizophrenia who were under antipsychotic polypharmacy treatment[61] or olanzapine is accounted for PR prolongation in a recent study.[57]

Findings about sudden death due to cardiomyopathy related with antipsychotic drug use in schizophrenia

In the literature, a widely accepted etiologic factor for cardiomyopathy is the use of clozapine. In a 11-year follow-up study, clozapine was found to be related with the lowest mortality rate and the fewest number of deaths due to ischemic cardiac disease than the most frequently used typical and atypical antipsychotic drugs.[60] Previously, the rate of clozapine-related cardiomyopathy had been considered to be similar to that within the normal population (8.9/100,000) in the USA.[61] Now, the rate of clozapine-induced cardiomyopathy is demonstrated to be five times more frequent than that in the normal population.[62] In a study after 10 years from the first described clozapine-induced cardiomyopathy, Reinders et al estimated the prevalence to be 9.6%. This relatively high rate may be the real rate of clozapine-related cardiomyopathy because of the increase in the awareness of the clinicians.[63] In case reports, usually myocarditis initiates within the first month of clozapine administration, independent from dosing with tachycardia, shortness of breath, cough, and fatigue symptoms in which 12.5%–24% may have mortal outcomes.[63,64] In the literature, there are few individual case reports on cardiomyopathy due to antipsychotic use such as amisulpride,[65] after quetiapine (n=3),[66–68] haloperidol,[69] and risperidone.[70]

Discussion

Similar to schizophrenia, metabolic syndrome and cardiovascular symptoms in schizophrenia are also multifactorial and associated with the influences of multiple genes in combination with environmental factors. NRG1 is a signaling protein that mediates cell–cell interactions, which is a shared development process in schizophrenia and cardiac function. Interestingly, the minor allele of the non-synonymous SNP rs10503929 within the *NRG1* gene was associated with sudden cardiac deaths. Functional polymorphisms in cytochrome P450, which play important roles in the metabolism of antipsychotic drugs, might be associated with prolongation of QTc.[71] The *SLC22A23* gene expression is in the development of heart[72] and SNPs in that the gene might be related with QT prolongation in some antipsychotics. However, there are some debates in genetic studies which were searching for the association of SNPs with schizophrenia: an association of polymorphism with schizophrenia might be a chance of observation, replication of the SNP findings are almost infrequent, the detected SNPs that are not specific to schizophrenia may also be involved in bipolar disorder, etc, in a relatively small sample size under psychiatric conditions (few hundreds to few thousands in GWAS vs >50,000 diabetes/cardiac studies). Thus, to boost the power of the associated SNPs in GWASs, some innovative statistical approaches are considered in recent studies aiming to neglect the need of larger and larger samples for detecting cardiovascular risk factors in schizophrenia,[73,74] although the richest findings from GWAS may still have very limited power to predict the genetic variation in schizophrenia.

In the last decade, a new window is opened after the discovery of the role of miRNAs to molecular pathology of schizophrenia with related implication for metabolic syndrome, being the target of antipsychotic drugs and interaction of neurotransmitters including serotonin–dopamine–glutamate. Changes in miRNA expression levels may reflect schizophrenia-related issues, conditions of high-risk individuals/first-episode psychotic, and/or intermediate targets of antipsychotic drug action that may lead to MetS, diabetes, and/or sudden cardiac death that are lacking in the literature. In addition, there are still no clinical and very few preclinical studies in association with miRNAs and after antipsychotic drug use. Thus, clarifying the potential role of miRNA in the pathophysiology of cardiovascular risks in schizophrenia might lead to the discovery of new therapeutic agents such as agonist miRNA (agomiR) or antagonist miRNA (antagomiR).

To clarify the related risk factors for increased MetS in patients with schizophrenia, drug-naïve patients or those who are at the very beginning stage of the illness and treatment seems crucial. In the literature, the findings seem far away

from a consistent conclusion about glucose tolerance or insulin resistance in first-episode and/or drug-naïve patients. In addition, there is no consensus about the inclusion criteria of the first-episode psychosis/schizophrenia. Usually, the first-episode studies do not prolong >1 year and high dropout rates in longer trials are major concerns. Meanwhile, inconclusive findings as impaired/non-impaired glucose tolerance or insulin resistance/no effect can be seen in the literature about first-episode and/or drug-naïve patients. However, a question rises about the slightly higher waist/hip ratio at the initial phase just prior to antipsychotic drugs that justify to be investigated.[1] Thus, we considered that the prevalence of MetS rate is not increased at the very beginning of the illness as prior to antipsychotic use that may give opportunity to clinicians for earlier interventions regarding prevention of cardiometabolic events. In addition to waist size, the duration of illness was found to be an important predictor for MetS in schizophrenia in a large-scale meta-analysis study in 2013.[27] Naturally, patients with first-episode psychosis are more frequently males than females, and females might be more liable to the metabolic side-effects of antipsychotic drugs and to the increment of waist circumference. Questionably, the antipsychotic drug use is increasing and reached top-selling drugs, surpassing lipid regulators or pump inhibitors in the USA in 2008.[33] Although, the pathophysiology underlying MetS due to antipsychotic use is not clear,[34] there are reasons to assume that treatment effects are related to the risk factors for cardiovascular problems. Interestingly, the studies about the influences of antipsychotics on cardiovascular problems do not exceed 1 year and patients who are compliant beyond 1 year might be underestimated. It is important to consider that individuals with schizophrenia may have a disadvantageous lifestyle that may lead to additional reasons for the development of MetS such as substance abuse, stress, inadequate self-care and unavailability of health care, financial problems, smoking, poor diet, low mobility, and lack of exercise, which are beyond this review.

According to the literature, to rank each antipsychotic for QTc prolongation risk seems difficult. Furthermore, the clinical significance for QT prolongation is unclear while QTc >450 ms or >30 ms prolongation of QTc versus baseline is widely accepted as important. Nevertheless, there are few studies investigating cardiac autonomic dysfunction prior to antipsychotic use or after introducing antipsychotic drugs in patients with first-episode psychosis in the literature. There is no reported case of TdP in therapeutic doses of antipsychotics except overdose conditions in the literature. Furthermore, the relation between atypical

or typical antipsychotics and sudden cardiac death was questioned after Ray et al's published registry-based study that had reported similar rates of sudden deaths between atypical and typical drugs.[75] However, this study is considerably criticized because of the definition of sudden death and inattentiveness for deaths due to secondary coronary-metabolic side effects. In general, atypical antipsychotics were thought to be safer than typical ones among the QTc interval or sudden deaths.[47] Although the possible mechanism in the sex difference in the QTc interval among various antipsychotics remains unclear, the serum testosterone level is accused for QTc interval differences.[76] However, in a few studies, no sex difference in QTc was demonstrated in various antipsychotic use such as depot, atypical, or typical;[49,54,55] thus there might be some other determinants of QTc changes such as age (particularly, >60 years), drug interactions, and serum electrolytes (ie, hypokalemia or hypomagnesemia).[56] Therefore, some new assessments might be conducted to determine the influences of antipsychotic drugs such as fragmented QRS or the T-wave peak to T-wave end (TpTe) interval and TpTe/QT, which have been accepted as predictors of ventricular arrhythmia more than QTc.[77] In addition, the influence of antipsychotics on atrial conduction is very limited that may be observed on the PR interval or P-wave dispersion.

In the literature, a widely accepted etiologic factor for cardiomyopathy is the use of clozapine. The clozapine-induced immunoglobin E (IgE)-mediated hypersensitivity reaction, hyper-eosinophilic syndrome with direct cardiotoxic effects of eosinophils through the blockade of the cholinergic M2 receptor, and importantly, increase in noradrenalin after clozapine use than other antipsychotics were accounted for the clozapine-induced cardiomyopathy.[64] In the literature, there are few individual case reports on cardiomyopathy due to other antipsychotics.

Conclusion

The studies and awareness about the physical needs of patients with schizophrenia are increasing, which had been neglected for a long time. The health care authorities or organizations are inviting physicians for increased cooperation and shared care between the different health care professionals to screen and treat CVD-risk factors, MetS, and diabetes in patients with psychiatric disorders because some risk factors of MetS or CVD are avoidable or at least modifiable to decrease high mortality in schizophrenia. These outcomes are reinforcing the importance of assessing all patients for cardiometabolic risk prior to and throughout treatment, choosing best fitting

antipsychotics, and monitoring cardiometabolic adverse effects. Thus, aiming to realize this serious challenge, further understanding of the underlying mechanisms and improved CVD prevention and treatment are needed. Finally, these future research groups should focus on conducting an integrated system of studies based on a holistic biopsychosocial evaluation.

Disclosure

The authors report no conflicts of interest in this work.

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