Schizophrenia
and type 2 diabetes mellitus

V. Mamakou,[1,2] A. Thanopoulou,[3] F. Gonidakis,[4]
N. Tentolouris,[5] V. Kontaxakis[4]

[1]Medical School, National and Kapodistrian University of Athens, Athens, [2]Dromokaiteio Psychiatric Hospital, Athens,
[3]Diabetes Centre, 2nd Department of Internal Medicine, Hippokration General Hospital, Medical School,
National and Kapodistrian University of Athens, Athens,
[4]1st Psychiatric Department, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens,
[5]First Department of Propaedeutic and Internal Medicine, National and Kapodistrian University of Athens,
Medical School, Laiko General Hospital, Athens, Greece

Schizophrenia is associated with increased risk for type 2 diabetes mellitus, resulting in elevated cardiovascular risk and limited life expectancy, translated into a weighted average of 14.5 years of potential life lost and an overall weighted average life expectancy of 64.7 years. The exact prevalence of type 2 diabetes among people with schizophrenia varies across studies and ranges 2–5fold higher than in the general population, whereas the aetiology is complex and multifactorial. Besides common diabetogenic factors, applied similarly in the general population, such as obesity, hyperlipidemia, smoking, hypertension, poor diet and limited physical activity, the co-occurrence of schizophrenia and diabetes is also attributed to unique conditions. Specifically, excessive sedentary lifestyle, social determinants, adverse effects of antipsychotic drugs and limited access to medical care are considered aggravating factors for diabetes onset and low quality of diabetes management. Schizophrenia itself is further proposed as causal factor for diabetes, given the observed higher prevalence of diabetes in young patients, newly diagnosed with schizophrenia and unexposed to antipsychotics. Furthermore, studies support genetic predisposition to diabetes among people with schizophrenia, suggesting shared genetic risk and disclosing a number of overlapped risk loci. Therefore, special attention should be paid in preventing diabetes in people with schizophrenia, through intervention in all possible modifiable risk factors. Implementation of careful antipsychotic prescription, provision of adequate motivation for balanced diet and physical activity and facilitating access to primary health care, could serve in reducing diabetes prevalence. On the other hand, increasing calls are made for early diagnosis of diabetes, application of the appropriate anti-diabetic therapy and strict inspection of therapy adherence, to limit the excess mortality due to cardiovascular events in people with schizophrenia. Moreover, population health programs could help counseling and preventing diabetes risk, additionally to early screening and diagnosis set, aiming to reduce disparities in populations. Finally, mental health-care providers might greatly promote offered health services to patients with schizophrenia, through a holistic individualized approach, considering additionally the physical health of the patients and working closely, preventively and therapeutically, in collaboration with the physicians and diabetologists.

Key words: Schizophrenia, type 2 diabetes, antipsychotics, prevention.

Introduction

The comorbidity between schizophrenia and increased prevalence of type 2 diabetes mellitus is well established in many different studies on clinical samples,[1,2] attributed to lifestyle habits and medications, as well as gene-environment interaction factors and shared susceptibility genetic loci for schizophrenia and type 2 diabetes mellitus.

Diabetes is a complex, chronic illness, requiring strict glycemic control beyond continuous medical care, with multifactorial risk-reduction strategies. Its prevalence among adults has risen from 4.7% in 1980 to 8.5% in 2014, more rapidly in middle- and low-income countries,[3] whereas similar increasing prevalence is observed among patients with schizophrenia.4 Therefore, interventions facilitating the knowledge, skills and abilities necessary to prevent, early diagnose and efficiently control diabetes are important. Promoting such steps could also serve moderate diabetes complications, such as blindness, kidney failure, heart attacks, stroke and lower limb amputation, contributing in limiting cardiovascular risk and mortality rates among people with schizophrenia. A search was conducted across Medline and Scopus and all relevant English articles referring to schizophrenia and type 2 diabetes mellitus (until June 2017) were reviewed.

Prevalence of Type 2 Diabetes among patients with Schizophrenia

The prevalence of diabetes in individuals with schizophrenia varies across different studies, reflecting increasing rates across years, methodological issues (sample size, methods of diabetes detection, inclusion or not of schizoaffective disorders in the case sample, longitudinal, cross-sectional, case-control, cohort, inpatient, outpatient studies), as well as age, sex, ethnicity disparities and further genetic and lifestyle particularities. However, most of them demonstrate elevated diabetes prevalence rates as compared with the general population, with odds estimated to be two to fine times elevated.[4]

Particularly, prevalence estimations of diabetes among patients with schizophrenia in the USA range from 14.2% in a retrospective cohort study,[5] 18.7% in a cross-sectional study conducted in 819 patients with schizophrenia,[6] to 23.3% in another cross-sectional with 2231 patients,[7] with an alarming trend of increase over time (6.9% in 1997 to 14.5% in 2004).[8] In the European populations, prevalence is evaluated 15% in the Netherlands,[9] 14.8% in a case-control study conducted in Sweden with 2.058.408 patients,[10] 22% in a cross-sectional study in Finland,[11] whereas the prevalence of diabetes among patients with schizophrenia in the UK is estimated to be 11.3%.[12] Similarly in Asia, prevalence approaches 15.3% in a case-control study in India,[13] 15% in Malaysia[14] and 8% in a case-control study in Singapore, however it included only 164 patients and 200 controls.[6] Accordingly, prevalence in Australia[15] reaches 12.1%. Redefining all causes contributing to excess diabetes comorbidity with schizophrenia constitutes the cornerstone to face the problem.

Clinical and lifestyle causes of Type 2 Diabetes in Schizophrenia

Various factors are involved in diabetes onset among patients with schizophrenia, which also apply in the general population. However they are observed more commonly in schizophrenia. Such factors are obesity, increasing age, hypertension, hyperlipidemia, smoking, lack of physical activity, poor diet, social determinants, poverty, quality of sleep, stress and sedentary lifestyle.

Most, but not all, patients with type 2 diabetes are overweight or obese, or present with an increased percentage of body fat, distributed predominantly in the abdominal region. Obesity is a common comorbidity in schizophrenia, with higher prevalence than the general population.[16] Even in first-episode schizophrenia, 22% of the patients were overweighed in a study conducted with 2548 patients.[17] Another study showed that patients diagnosed with schizophrenia were overweight-obese (45–55%, RR: 1.5–2), smokers (50–80%, RR: 2–3), had diabetes (10–15%, RR: 2), hypertension (19–58%, RR: 2–3), dyslipidemia (25–69% RR: 5) and metabolic syndrome (37–63%, RR: 2–3).[18] Additionally, it has been observed rates of BMI greater than 27 to reach 42% in a group of individuals with schizophrenia, compared to 27% in the general population.[19]

Poor diet and physical inactivity[20] result in increased diabetes rates among people with schizophrenia. Deficits in fruits and vegetables intake, excess of fat, sugar and fast food consume characterize the dietary components often preferred by patients with schizo-

phrenia.[21,22] Several studies report poor nutritional quality[23–27] with relevant impact on weigh gain and further cardiometabolic adverse effects. Another study estimated the mean number of fruit and vegetable portions per day at 2.8±1.8, whereas over a third patients did not eat any fruit in a typical week.[28] However, choices of poor dietary preferences are likely related to unemployment, household income and lower socioeconomic status, not adequate supportive family environment, cognitive deficits and educational limitations. Homelessness often accompanies patients with schizophrenia, setting many barriers to diabetes prevention, including food insecurity, literacy and numeracy deficiencies, lack of insurance and cognitive dysfunction.[29] Access to health care services for individuals with schizophrenia is often inhibitory by perplexed and bureaucratic health service procedures, unequal legislations, as well as communities' and health providers' racism against persons with mental issues.

Furthermore, negative symptoms,[20] sedating effects of antipsychotic medications and obesity[30] contribute to restricted physical activity of individuals with schizophrenia. Engagement in moderate physical activity is reported less frequently in schizophrenia group than the National Health and Nutrition Examination Surveys group (NHANES group).[31] Specifically, few individuals with schizophrenia reported vigorous physical activity, whereas less than half of the sample followed moderate physical activity. Similar findings are observed by other studies,[32] while a systematic review reported linkage of impaired physical activity with limited socioeconomic status.[33] Besides exercise, sleep alterations, often meet in people with schizophrenia,[34–36] due to desynchronization between melatonin profiles and the sleep–wake rhythms,[34,37–39] body temperature,[39] and levels of tryptophan and prolactin,[40] might play a role on diabetes onset. The disturbed circadian clock underlying in schizophrenia[41–43] contributes to the development of metabolic disorders, affecting further the stress axis (hypothalamic-pituitary-adrenal axis, glucocorticoids, interaction with leptin), the motivation and reward system (dopamine, interaction with hypothalamic-pituitary-adrenal axis) and the orexin/melanin concentrating hormone neuronal network.[44]

Additionally, smoking, a known risk factor for type 2 diabetes, among people with schizophrenia is cal-

culated 5.6 times as much as people without,[45,46] thus increasing the risk for diabetes and its treatment outcome. Likewise, a study estimated smoking rates at 64.9% among people with schizophrenia and in an increased number of them cigarette use was heavy.[28] Additionally to smoking, hypertension and hyperlipidemia contribute to elevated diabetes risk.[47] A cohort study of 2270 patients from 16 European countries reported 69.6% hyperlipidemia rates and 43.4% for hypertension,[25] while the risk was estimated 5fold and 2-3fold higher for these condition respectively, in comparison with the general population.[48] Moreover, odds ratio (OR) of diabetes onset in patients with schizophrenia and hypertension or dyslipidemia, in comparison with patients with schizophrenia without this comorbidity, are reported to be 3.23 [95% Confidence Interval (CI) 2.04–5.11] and 5.99 (3.87–8.92) respectively.[15] Furthermore, hazard ratio for earlier diabetes onset time is evaluated 1.87 (95% CI 1.12–3.09) and 4.67 (2.19–10.00) for patients with schizophrenia under antihypertensive and lipid-lowering treatment respectively.[49]

Finally, environmental loading is proposed as an etiological factor for diabetes and schizophrenia co-occurrence, influencing susceptibility to both conditions. For instance, poverty and lower educational chances are linked to schizophrenia and obesity.[50] Both increased rates of impaired glucose tolerance and schizophrenia was detected in the cohort born during the Dutch famine[51] in 1944–1945 vitamin D deficit during early life is associated with risk of schizophrenia,[52,53] whereas it also influences the insulin response to glucose stimulation, although its limited impact on basal insulinemia.[54,55]

Medication, Schizophrenia and Type 2 Diabetes

There is a considerable literature on the metabolic adverse effects of antipsychotic agents. In particular, comparison between second generation antipsychotics (SGA) with first generation antipsychotics (FGA) revealed a 1.3 fold elevated risk for diabetes.[56] This effect is intermediated either by weight gain, or –at 25% of cases[57]– though direct impairment in glucose homeostasis, potentially via blockade of central and peripheral muscarinic M3 receptors.[58,59] M3 receptors are widely expressed in the brain (ventromedial hypothalamic and arcuate nuclei of the hypothalamus,

dorsal vagal complex of the brainstem)[60, 61] effecting insulin and glucagon secretion, glucose homeostasis and body weight regulation,[62, 63] as well as on pancreatic beta cells, modulating the acetylcholine pathway for insulin secretion.[64,65] Antipsychotic affinity for the M3 receptors is considered the best indicator for diabetogenic liability.[66,67] Interestingly, olanzapine and clozapine have a profile to potently block the M3 receptors, while antipsychotics with a lower risk of metabolic dysfunction side-effect, such as risperidone and ziprasidone, have little effect on the M3 receptors.[67,68]

Another study detected elevated risk of diabetes in both patients treated with SGA (adjusted hazard ratio [HR] 1.32, 95% CI 1.01–1.75) and those treated with FGA (adjusted HR 1.82, 95% CI 1.30–2.55) against control patients without schizophrenia.[69] Furthermore, a meta-analysis on the prevalence of diabetes reported 2.1% diabetes prevalence among antipsychotic-naïve patients, whereas the prevalence was 12.8% for antipsychotic receivers.[17] However, a systematic review of 22 prospective, randomized, control trials, though short-term followed, detected no difference in glycemic abnormalities between placebo and antipsychotic cohorts.[70] Suggested explanations to those inconsistent findings are beyond methodological problems such as medication pre-exposure of tested groups, duration and dose of medication receive, severity, duration and type of schizophrenia, way of diabetes diagnosis (self-report, anti-diabetes drugs, ADA criteria), homogeneity of case group (schizophrenia, schizoaffective disorders, psychosis), adherence to antipsychotic receive, follow-up period and other unobserved confounding, also the heterogeneity among SGA and FGA groups.

Therefore, other studies attempted to evaluate the diabetogenic role of each antipsychotic regiment separately. Particularly, a large, population-based study conducted in Denmark with 345,937 cases treated with antipsychotics and 1,426,488 controls found 1.45% for clozapine, 1.29% for olanzapine and 1.23% for risperidone, 1.94% for sertindole, 1.57% for perphenazine, 1.94% for ziprasidone and even 1.17 for haloperidol increased diabetes risk,[71] whereas no increase in diabetes risk was detected for aripiprazole, amisulpride or quetiapine. On the other hand, a study on newly-onset schizophrenia patients revealed diabetes incidence patients with olanzapine initiation therapy (hazard ratio, HR=1.41) and with mid-potency

conventional antipsychotics (HR=1.60).[49] Moreover, an FDA's database analysis in terms of diabetes, reported the following adjusted ratios hierarchy for diabetes-mellitus-related adverse outcomes: olanzapine 9.6 (95% CI 9.2–10.0), risperidone 3.8 (3.5–4.1), quetiapine 3.5 (3.2–3.9), clozapine 3.1 (2.9–3.3), ziprasidone 2.4 (2.0–2.9) aripiprazole 2.4 (1.9–2.9) and haloperidol 2.0 (1.7–2.3).[72] Clozapine and olanzapine are consistently associated with greater weight gain risk.[73]

Further, antidepressants may attribute to increased diabetes risk. Probable suggested mechanisms are their sedative effect, the increase in appetite, and weight gain.[74–76] A meta-analysis, though included only observational studies, reported increase in diabetes onset likelihood (OR 51.50, 95% CI 1.08–2.10, HR 51.19, 95% CI: 1.08–1.32).[77] However, most studies[78,79] provide evidence for elevated diabetes risk with the concurrent use of tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) (OR=1.89),[80] the long-term use of both tricyclic antidepressants (incidence rate ratio, IRR=1.77) and SSRIs (IRR=2.06) in at least moderate daily doses,[81] as well as the use of antidepressants medication in high-risk patients.[82] Further, amitriptyline, imipramide and mirtazapine are associated substantially with weight gain, nortriptyline and paroxetine appear to have intermediate effect, whereas bupropion and fluoxetine are linked with weight loss.[48]

Additionally, mood stabilizers, especially valproate itself[83] and lithium,[84] have been associated with insulin resistance and diabetes risk,[22,85] related possibly to weight gain,[86] and/or fatty liver infiltration.[87] However, little research has been performed in terms of concomitant application of different categories of medications[88,89] to reveal potential synergic action. One of those[89] conducted in Medicaid-enrolled youths, reported higher risk for diabetes incident for SGA initiators concomitantly to antidepressant use (OR .54, 95% CI 1.17–2.03, p=0.002), when compared to only SGA initiators. Further, first-episode and antipsychotic-naïve patients with schizophrenia as compared to chronic patients, are more vulnerable to severe weight gain, rapidly during the first few weeks, due to antipsychotics.[79]

Antipsychotics are associated with lipid abnormalities and thus could increase diabetes risk.[48,90] On the contrary, most of antidepressants[91] as well as lithium[92] observe no associated with dyslipidemia. Valproate

has been associated increased triglycerides and glucose, and insulin abnormalities.[93] Antipsychotics are not associated with hypertension, potentially due their alpha-1 blocking effects,[94] which can lower blood pressure. Among antidepressants, venlafaxine is most frequently associated with elevated blood pressure,[95] while mirtazapine has been found to be associated less than tricyclic antidepressants.[96] Generally, mood stabilizers have no effect on blood pressure, apart from chronic renal failure related to lithium volume distribution.

Genetic predisposition for comorbidity Schizophrenia and Type 2 Diabetes

Metabolic loading in patients with schizophrenia, such as dyslipidemia and insulin resistance, presents also prior to treatment onset,[97–99] implying genetic vulnerability. Henry Maudsley[112] already proposed the genetic link between diabetes and schizophrenia in his 1897 textbook "The Pathology of Mind". Prevalence of diabetes is estimated 1.27–1.63 fold higher in medication-naïve patients with schizophrenia as compared with the general population in the Netherlands.[100] Furthermore, similarly increased levels of IL-1β, IL-6, TNF-α, but also importantly elevated adiponectin levels were detected in drug naïve, first episode patients with schizophrenia and normal weight, as compared with obese or overweight individuals without schizophrenia, which suggest a potential unique pro-inflammatory role of adiponectin in patients with schizophrenia, leading to later metabolic syndrome.[101]

To explain this comorbidity between schizophrenia and diabetes in genetic terms, linkage studies as well as genome-wide association studies (GWAS) are applied to shed light into this direction. As linkage studies are concerned, one could start with probing the gene involved in both glucose and dopamine pathways. According to the data queried from Genetic Association Database[102] (http://geneticassociationdb. nih.gov/), a total of 37 common genes are detected across these susceptibility genes of schizophrenia and diabetes. For instance, chromosome 1q may harbor genes influencing working memory[103] and diabetes-related traits.[104] Moreover, association studies suggest that chromosome 1q21-24 may harbor risk genes for diabetes.[105] Among others, genes with involvement in both glucose metabolism and cognitive function

which may increase the risk of diabetes in patients with schizophrenia vice-versa, are proposed to be nitric oxide synthase 1 (neuronal) adapter, aka, carboxylterminal PDZ ligand of neuronal nitric oxide synthase protein (CAPON), Nitric oxide synthase 1 adaptor protein (NOS1AP), glycogen synthase kinase 3 gene GSK-3, catecholamine O-transferase gene COMT, tyrosine hydroxylase (TH) gene.[106] Association findings further support that TCF7L2, which is responsible for diabetes, increases risk of schizophrenia in two further studies.[107,108] Web-based catalog for published genome-wide association studies (GWAS) to search for overlapped findings for diabetes and schizophrenia[109] provided no evidence for shared etiology (with a significance level of p<10⁻8). Proposed explanation therefore is that the genetic overlap for schizophrenia and diabetes may depend on combination of rare variants with small effect acting in concert to cause both diseases or to variants other than single nucleotide polymorphisms (SNPs).[106] Another GWAS analysis failed to detect risk variants associating schizophrenia with diabetes in a Japanese population.[110] Moreover, pathway analysis retrieved 2,104 proteins, 364 of them found simultaneously interacting with susceptibility proteins of both diabetes and schizophrenia, therefore proposed as new candidate risk factors for both diseases.[111]

Prevention and therapy

Clinical practice guidelines and individualized medicine are keys to improve health of patients with schizophrenia. The American Diabetes Association (ADA) highlights the importance of patient-centered care, defined as care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions. Annual screening for people with schizophrenia for prediabetes or diabetes is recommended. Changes in weight, glycemic control, blood pressure and cholesterol levels should be carefully monitored and the treatment regimen should be reassessed.[29]

Motivation in the direction of healthy lifestyle choices, such as healthy eating, physical activity, tobacco cessation, weight management and effective strategies for coping with stress, should belong to health providers' priorities. Providers should assess social context, including potential food insecurity, housing stability, and financial barriers, and apply that infor-

mation to treatment decisions. Patients should be referred to local community resources when available and provided with self-management support from health coaches, navigators, or community health workers when available.[29]

Finally, collaborative, multidisciplinary teams are best suited to provide care for people with chronic conditions such as diabetes and to facilitate patients' self-management. The care team, which includes the patient, should prioritize timely and appropriate intensification of lifestyle and/or pharmacological therapy for patients who have not achieved the rec-ommended metabolic targets. Redefining the roles of the health care delivery team and empowering patient self-management are fundamental to achieve diabetes prevention and bring optimal therapeutic results.[29]

Conclusion

Coordinated management of diabetes or prediabetes and schizophrenia is recommended to prevent diabetes onset and achieve diabetes treatment targets, promoting equal health services and reducing disparities in populations.

Σχιζοφρένεια
και σακχαρώδης διαβήτης τύπου 2

Β. Μαμάκου,[1,2] Α. Θανοπούλου,[3] Φ. Γονιδάκης,[4]
Ν. Τεντολούρης,[5] Β. Κονταξάκης[4]

[1]Ιατρική Σχολή, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών, Αθήνα,
[2]Δρομοκαΐτειο Ψυχιατρικό Νοσοκομείο Αθηνών, Αθήνα,
[3]Διαβητολογικό Κέντρο, Β΄ Παθολογική Κλινική Πανεπιστημίου Αθηνών, Ιπποκράτειο Γενικό Νοσοκομείο Αθηνών, ΕΚΠΑ,
[4]Α΄ Ψυχιατρική Κλινική, Αιγινήτειο Νοσοκομείο, ΕΚΠΑ,
[5]Α' Προπαιδευτική Παθολογική Κλινική Πανεπιστημίου Αθηνών, Νοσοκομείο Λαϊκό, ΕΚΠΑ, Αθήνα

Η σχιζοφρένεια συνδέεται με αυξημένο κίνδυνο για εμφάνιση σακχαρώδους διαβήτη τύπου 2, συμβάλλοντας σε επίταση του καρδιαγγειακού κινδύνου και περιορισμό του προσδόκιμου επιβίωσης σε ασθενείς με σχιζοφρένεια. Σε ό,τι αφορά στο προσδόκιμο ζωής, αυτό ανέρχεται συνολικά σε 14,5 έτη πιθανής απώλειας ζωής και συνολικό μέσων όρο προσδόκιμου ζωής τα 64,7 έτη. Ο ακριβής επιπολασμός του διαβήτη τύπου 2 στα άτομα με σχιζοφρένεια διαφέρει στις μελέτες και κυμαίνεται από 2–5 φορές υψηλότερος σε σχέση με τον γενικό πληθυσμό. Η αιτιολογία του σακχαρώδους διαβήτη τύπου 2 στους ασθενείς με σχιζοφρένεια είναι πολύπλοκη και πολυπαραγοντική. Εκτός από τους κοινούς διαβητογόνους παράγοντες, που απαντώνται και στον γενικό πληθυσμό, όπως η παχυσαρκία, η υπερλιπιδαιμία, το κάπνισμα, η υπέρταση, η κακή διατροφή και η περιορισμένη σωματική δραστηριότητα, η συνύπαρξη σχιζοφρένειας και διαβήτη αποδίδεται σε επιπλέον ιδιαίτερους παράγοντες. Συγκεκριμένα, ο καθιστικός τρόπος ζωής, κοινωνικοοικονομικοί παράγοντες, οι ανεπιθύμητες ενέργειες των αντιψυχωτικών φαρμάκων και η περιορισμένη πρόσβαση στις υπηρεσίες υγείας θεωρούνται επιβαρυντικοί παράγοντες για την εμφάνιση του διαβήτη και τη χαμηλή ποιότητα διαχείρισής του. Η ίδια η σχιζοφρένεια θεωρείται αιτιολογικός παράγοντας για εμφάνιση σακχαρώδους διαβήτη, δεδομένου του παρατηρούμενου υψηλότερου επιπολασμού του διαβήτη σε νεαρούς ασθενείς, που έχουν πρόσφατα διαγνωσθεί με σχιζοφρένεια και δεν έχουν εκτεθεί σε αντιψυχωτικά. Επιπλέον, οι μελέτες υποστηρίζουν γενετική προδιάθεση για διαβήτη μεταξύ των ατόμων με σχιζοφρένεια, υποδηλώνοντας ότι κοινοί γενετικοί παράγοντες ευθύνονται τόσο για τη σχιζοφρένεια όσο και για τον σακχαρώδη διαβήτη, ενώ έχει προσδιορισθεί ένας αριθμός αλληλεπικαλυπτόμενων υπεύθυνων

γονιδίων. Ως εκ τούτου, πρέπει να δοθεί ιδιαίτερη προσοχή στην πρόληψη του διαβήτη σε άτομα με σχιζοφρένεια μέσω παρέμβασης σε όλους τους δυνατούς τροποποιήσιμους παράγοντες κινδύνου. Η εφαρμογή κατάλληλης αντιψυχωτικής αγωγής, η παροχή επαρκών κινήτρων για ισορροπημένη διατροφή και φυσική δραστηριότητα και η διευκόλυνση της πρόσβασης στις υπηρεσίες υγείας, θα μπορούσαν να χρησιμεύσουν στη μείωση του επιπολασμού του διαβήτη. Από την άλλη πλευρά, γίνεται ακόμα πιο επιτακτική η έγκαιρη διάγνωση του διαβήτη, η εφαρμογή κατάλληλης αντιδιαβητικής θεραπείας και η αυστηρή επίβλεψη της συμμόρφωσης στη θεραπεία, για τον περιορισμό της αυξημένης θνησιμότητας λόγω καρδιαγγειακών επεισοδίων σε άτομα με σχιζοφρένεια. Επιπλέον, τα προγράμματα υγείας πληθυσμού θα μπορούσαν να βοηθήσουν στην παροχή ενημέρωσης, συμβουλών και στην πρόληψη του κινδύνου διαβήτη, παράλληλα με τον έγκαιρο έλεγχο του πληθυσμού και την πρώιμη διάγνωση, περιορίζοντας πληθυσμιακές ανισότητες. Τέλος, οι πάροχοι υπηρεσιών ψυχικής υγείας θα μπορούσαν να βελτιώσουν σημαντικά την ποιότητα της προσφερόμενης θεραπείας σε ασθενείς με σχιζοφρένεια, μέσω μιας ολιστικής εξατομικευμένης προσέγγισης, λαμβάνοντας σοβαρά υπόψη και τη σωματική υγεία των ασθενών μέσα από τη στενή συνεργασία και σε πλαίσια τόσο πρόληψης όσο και θεραπείας, με παθολόγους και διαβητολόγους.

Λέξεις ευρετηρίου: Σχιζοφρένεια, διαβήτης τύπου 2, αντιψυχωσικά φάρμακα, πρόληψη.

References

1. Rado J. *The Complex Inter-relationship between Diabetes and Schizophrenia*. Current diabetes reviews, 2016

2. Sugai T, Suzuki Y, Yamazaki M, Shimoda K, Mori T, Ozeki Y et al. High Prevalence of Obesity, Hypertension, Hyperlipidemia, and Diabetes Mellitus in Japanese Outpatients with Schizophrenia: A Nationwide Survey. *PloS One* 2016, 11:e0166429. doi: 10.1371/journal.pone.0166429

3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine* 2006, 3:e442, doi: 10.1371/journal.pmed.0030442

4. Suvisaari J, Keinanen J, Eskelinen S, Mantere O. Diabetes and Schizophrenia. *Curr Diabet Report* 2016, 16:16, doi: 10.1007/s11892-015-0704-4

5. Lamberti JS, Crilly JF, Maharaj K, Olson D, Wiener K, Dvorin S et al. Prevalence of diabetes mellitus among outpatients with severe mental disorders receiving atypical antipsychotic drugs. *J Clin Psychiatry* 2004, 65:702–706

6. Bell RC, Farmer S, Ries R, Srebnik D. Metabolic risk factors among medicaid outpatients with schizophrenia receiving second-generation antipsychotics. *Psychiatr Serv* 2009, 60:1686–1689, doi: 10.1176/ps.2009.60.12.1686

7. Jerrell JM, McIntyre RS, Tripathi A. Incidence and costs of cardiometabolic conditions in patients with schizophrenia treated with antipsychotic medications. *Clin Schizophr Relat Psychos* 2010, 4:161–168, doi: 10.3371/CSRP.4.3.2

8. Citrome L, Jaffe A, Levine J, Martello D. Incidence, prevalence, and surveillance for diabetes in New York State psychiatric hospitals, 1997–2004. *Psychiatr Serv* 2006, 57:1132–1139, doi: 10.1176/ps.2006.57.8.1132

9. Mookhoek EJ, de Vries WA, Hovens JE, Brouwers JR, Loonen AJ. Risk factors for overweight and diabetes mellitus in residential psychiatric patients. *Obes Facts* 2011, 4:341–345, doi: 10.1159/000333420

10. Wandell P, Ljunggren G, Wahlstrom L, Carlsson AC. Diabetes and psychiatric illness in the total population of Stockholm. *J Psychosomat Research* 2014, 77:169–73, doi: 10.1016/j.jpsychores.2014.06.012

11. Suvisaari J, Perala J, Saarni SI, Harkanen T, Pirkola S, Joukamaa M et al. Type 2 diabetes among persons with schizophrenia and other psychotic disorders in a general population survey. *Eur Arch Psychiatr Clinl Neurosci* 2008, 258:129–136

12. Schoepf D, Potluri R, Uppal H, Natalwala A, Narendran P, Heun R. Type-2 diabetes mellitus in schizophrenia: increased prevalence and major risk factor of excess mortality in a naturalistic 7-year follow-up. *Eur Psychiatry* 2012, 27:33–42, doi: 10.1016/j.eurpsy.2011.02.009

13. Subashini R, Deepa M, Padmavati R, Thara R, Mohan V. Prevalence of diabetes, obesity, and metabolic syndrome in subjects with and without schizophrenia (CURES-104). *J Postgrad Med* 2011, 57:272–277, doi: 10.4103/0022-3859.90075

14. Fairuz AR, Maniam T, Khalid BA. Prevalence of insulin resistance in schizophrenia in HUKM. *Med J Malaysia* 2007, 62:290–293

15. Foley DL, Mackinnon A, Morgan VA, Watts GF, McGrath JJ, Castle DJ et al. Predictors of type 2 diabetes in a nationally representative sample of adults with psychosis. *World Psychiatry* 2014, 13:176–183, doi: 10.1002/wps.20130

16. Li Q, Du X, Zhang Y, Yin G, Zhang G, Walss-Bass C et al. The prevalence, risk factors and clinical correlates of obesity in Chinese patients with schizophrenia. *Psychiatry Res* 2017, 251:131–136, doi: 10.1016/j.psychres.2016.12.041

17. Mitchell AJ, Vancampfort D, De Herdt A, Yu W, De Hert M. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. *Schizophr Bull* 2013, 39:295–305, doi: 10.1093/schbul/sbs082

18. Correll CU. Balancing efficacy and safety in treatment with antipsychotics. *CNS spectrums* 2007, 12(Suppl 17):12–20, 35

19. Allison DB, Fontaine KR, Heo M, Mentore JL, Cappelleri JC, Chandler LP et al. The distribution of body mass index among individuals with and without schizophrenia. *J Clin Psychiatry* 1999, 60:215–220

20. Vancampfort D, Knapen J, Probst M, van Winkel R, Deckx S, Maurissen K et al. Considering a frame of reference for physical activity research related to the cardiometabolic risk profile in

schizophrenia. *Psychiatry Res* 2010, 177:271–279, doi: 10.1016/j.psychres.2010.03.011

21. Brown S, Birtwistle J, Roe L, Thompson C. The unhealthy lifestyle of people with schizophrenia. *Psychol Med* 1999, 29:697–701

22. McCreadie RG, Scottish Schizophrenia Lifestyle G. Diet, smoking and cardiovascular risk in people with schizophrenia: descriptive study. *Br J Psychiatry* 2003, 183:534–539

23. Hahn LA, Galletly CA, Foley DL, Mackinnon A, Watts GF, Castle DJ et al. Inadequate fruit and vegetable intake in people with psychosis. *Aust N Zeal J Psychiatry* 2014, 48:1025–1035, doi: 10.1177/0004867414553950

24. Gupta A, Craig TK. Diet, smoking and cardiovascular risk in schizophrenia in high and low care supported housing. *Epidemiol Psichiatria Sociale* 2009, 18:200–207

25. De Hert M, Mauri M, Shaw K, Wetterling T, Doble A, Giudicelli A et al. The METEOR study of diabetes and other metabolic disorders in patients with schizophrenia treated with antipsychotic drugs. I. Methodology. *Intern J Meth Psychiatr Research* 2010, 19:195–210, doi: 10.1002/mpr.322

26. Strassnig M, Brar JS, Ganguli R. Nutritional assessment of patients with schizophrenia: a preliminary study. *Schizophr Bull* 2003, 29:393–397

27. Henderson DC, Borba CP, Daley TB, Boxill R, Nguyen DD, Culhane MA et al. Dietary intake profile of patients with schizophrenia. *Ann Clin Psychiatry* 2006, 18:99–105, doi: 10.1080/10401230600614538

28. Heald A, Pendlebury J, Anderson S, Narayan V, Guy M, Gibson M et al. Lifestyle factors and the metabolic syndrome in Schizophrenia: a cross-sectional study. *Ann Gen Psychiatry* 2017, 16:12, doi: 10.1186/s12991-017-0134-6

29. Standards of Medical Care in Diabetes-2017: Summary of Revisions. *Diabet Care* 2017, 40(Suppl 1):S4–S5, doi: 10.2337/dc17-S003

30. Vancampfort D, Sweers K, Probst M, Maurissen K, Knapen J, Minguet P et al. Association of the metabolic syndrome with physical activity performance in patients with schizophrenia. *Diabet Metabol* 2011, 37:318–323, doi: 10.1016/j.diabet.2010.12.007

31. Ratliff JC, Palmese LB, Reutenauer EL, Liskov E, Grilo CM, Tek C. The effect of dietary and physical activity pattern on metabolic profile in individuals with schizophrenia: a cross-sectional study. *Compr Psychiatry* 2012, 53:1028–1033, doi: 10.1016/j.comppsych.2012.02.003

32. Faulkner G, Cohn T, Remington G. Validation of a physical activity assessment tool for individuals with schizophrenia. *Schizophr Res* 2006, 82:225–231, doi: 10.1016/j.schres.2005.10.020

33. Vancampfort D, Knapen J, Probst M, Scheewe T, Remans S, De Hert M. A systematic review of correlates of physical activity in patients with schizophrenia. *Acta Psychiatr Scand* 2012, 125:352–362, doi: 10.1111/j.16000447.2011.01814.x

34. Wulff K, Dijk DJ, Middleton B, Foster RG, Joyce EM. Sleep and circadian rhythm disruption in schizophrenia. *Br J Psychiatry* 2012, 200:308–316, doi: 10.1192/bjp.bp.111.096321

35. Monti JM, BaHammam AS, Pandi-Perumal SR, Bromundt V, Spence DW, Cardinali DP et al. Sleep and circadian rhythm dysregulation in schizophrenia. *Progr Neuro-psychopharmacol Biol Psychiatry* 2013, 43:209–216, doi: 10.1016/j.pnpbp. 2012.12.021

36. Chouinard S, Poulin J, Stip E, Godbout R. Sleep in untreated patients with schizophrenia: a meta-analysis. *Schizophr Bull* 2004, 30:957–967

37. Afonso P, Figueira ML, Paiva T. Sleep-promoting action of the endogenous melatonin in schizophrenia compared to healthy controls. *Int J Psychiatry Clin Pract* 2011, 15:311–315, doi: 10.3109/13651501.2011.605954

38. Bromundt V, Koster M, Georgiev-Kill A, Opwis K, Wirz-Justice A, Stoppe G et al. Sleep-wake cycles and cognitive functioning in schizophrenia. *Br J Psychiatry* 2011, 198:269–276, doi: 10.1192/bjp.bp.110.078022

39. Morgan R, Cheadle AJ. Circadian body temperature in chronic schizophrenia. *Br J Psychiatry* 1976, 129:350–354

40. Rao ML, Gross G, Strebel B, Halaris A, Huber G, Braunig P et al. Circadian rhythm of tryptophan, serotonin, melatonin, and pituitary hormones in schizophrenia. *Biol Psychiatry* 1994, 35:151–163

41. Levitan RD, Davis C, Kaplan AS, Arenovich T, Phillips DI, Ravindran AV. Obesity comorbidity in unipolar major depressive disorder: refining the core phenotype. *J Clin Psychiatry* 2012, 73:1119–1124, doi: 10.4088/JCP.11m07394

42. Mansur RB, Brietzke E, McIntyre RS. Is there a "metabolic-mood syndrome"? A review of the relationship between obesity and mood disorders. *Neurosci Biobehavl Rev* 2015, 52:89–104, doi: 10.1016/j.neubiorev.2014.12.017

43. Vogelzangs N, Beekman AT, Boelhouwer IG, Bandinelli S, Milaneschi Y, Ferrucci L et al. Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. *J Clin Psychiatry* 2011, 72:598–604, doi: 10.4088/JCP.10m06559

44. Barandas R, Landgraf D, McCarthy MJ, Welsh DK. Circadian Clocks as Modulators of Metabolic Comorbidity in Psychiatric Disorders. *Curr Psychiatry Rep* 2015, 17:98, doi: 10.1007/s11920-015-0637-2

45. Muller DP, de Haan L. Smoking cessation and schizophrenia. *Tijdschrift voor psychiatrie* 2017, 59:297–301

46. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* 2005, 76:135–157, doi: 10.1016/j.schres.2005.02.010

47. Ward M, Druss B. The epidemiology of diabetes in psychotic disorders. *Lancet Psychiatry* 2015, 2:431–451, doi: 10.1016/S2215-0366(15)00007-3

48. De Hert M, Cohen D, Bobes J, Cetkovich-Bakmas M, Leucht S, Ndetei DM et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. *World Psychiatry* 2011, 10:138–151

49. Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naive schizophrenia patients. *Neuropsychopharmacology* 2010, 35:1997–2004, doi: 10.1038/npp.2010.78

50. Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A et al. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull* 2000, 26:903–912

51. Kyle UG, Pichard C. The Dutch Famine of 1944–1945: a pathophysiological model of long-term consequences of wasting disease. *Curr Opin Clin Nutr Metabol Care* 2006, 9:388–394, doi: 10.1097/01.mco.0000232898.74415.42

52. McGrath J, Saari K, Hakko H, Jokelainen J, Jones P, Jarvelin MR et al. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. *Schizophr Res* 2004, 67:237–245, doi: 10.1016/j.schres.2003.08.005

53. Brown AS, Susser ES. Prenatal nutritional deficiency and risk of adult schizophrenia. *Schizophr Bull* 2008, 34:1054–63, doi: 10.1093/schbul/sbn096

54. Zeitz U, Weber K, Soegiarto DW, Wolf E, Balling R, Erben RG. Impaired insulin secretory capacity in mice lacking a functional

vitamin D receptor. *FASEB J* 2003, 17:509-11, doi: 10.1096/fj.02–0424fje

55. Bourlon PM, Faure-Dussert A, Billaudel B. The de novo synthesis of numerous proteins is decreased during vitamin D3 deficiency and is gradually restored by 1, 25-dihydroxyvitamin D3 repletion in the islets of langerhans of rats. *J Endocrinol* 1999, 162:101–109

56. Smith M, Hopkins D, Peveler RC, Holt RI, Woodward M, Ismail K. First- v. second-generation antipsychotics and risk for diabetes in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2008, 192:406–411, doi: 10.1192/bjp.bp.107.037184

57. Scheen AJ, De Hert MA. Abnormal glucose metabolism in patients treated with antipsychotics. *Diabet Metabolism* 2007, 33:169–175, doi: 10.1016/j.diabet.2007.01.003

58. Deng C. Effects of antipsychotic medications on appetite, weight, and insulin resistance. *Endocrinol Metab Clin North Am* 2013, 42:545–563, doi: 10.1016/j.ecl.2013.05.006

59. Weston-Green K, Huang XF, Deng C. Second generation antipsychotic-induced type 2 diabetes: a role for the muscarinic M3 receptor. *CNS Drugs* 2013, 27:1069–1080, doi: 10.1007/s40263-013-0115-5

60. Levey AI, Edmunds SM, Heilman CJ, Desmond TJ, Frey KA. Localization of muscarinic m3 receptor protein and M3 receptor binding in rat brain. *Neuroscience* 1994, 63:207–221

61. Zubieta JK, Frey KA. Autoradiographic mapping of M3 muscarinic receptors in the rat brain. *J Pharmacol Experiment Therap* 1993, 264:415–422

62. Buijs RM, Chun SJ, Niijima A, Romijn HJ, Nagai K. Parasympathetic and sympathetic control of the pancreas: a role for the suprachiasmatic nucleus and other hypothalamic centers that are involved in the regulation of food intake. *J Comparat Neurol* 2001, 431:405–423

63. Li Y, Wu X, Zhu J, Yan J, Owyang C. Hypothalamic regulation of pancreatic secretion is mediated by central cholinergic pathways in the rat. *J Physiol* 2003, 552:571–587, doi: 10.1113/jphysiol.2003.049122

64. Gautam D, Gavrilova O, Jeon J, Pack S, Jou W, Cui Y et al. Beneficial metabolic effects of M3 muscarinic acetylcholine receptor deficiency. *Cell Metabolism* 2006, 4:363–375, doi: 10.1016/j.cmet.2006.09.008

65. Gautam D, Ruiz de Azua I, Li JH, Guettier JM, Heard T, Cui Y et al. Beneficial metabolic effects caused by persistent activation of beta-cell M3 muscarinic acetylcholine receptors in transgenic mice. *Endocrinology* 2010, 151:5185–94, doi: 10.1210/en.2010-0519

66. Silvestre JS, Prous J. Research on adverse drug events. I. Muscarinic M3 receptor binding affinity could predict the risk of antipsychotics to induce type 2 diabetes. *Meth Find Exp Clin Pharmacol* 2005, 27:289–304, doi: 10.1358/mf.2005.27.5.908643

67. Johnson DE, Yamazaki H, Ward KM, Schmidt AW, Lebel WS, Treadway JL et al. Inhibitory effects of antipsychotics on carbachol-enhanced insulin secretion from perifused rat islets: role of muscarinic antagonism in antipsychotic-induced diabetes and hyperglycemia. *Diabetes* 2005, 54:1552–1558

68. Weston-Green K, Huang XF, Lian J, Deng C. Effects of olanzapine on muscarinic M3 receptor binding density in the brain relates to weight gain, plasma insulin and metabolic hormone levels. *Eur Neuropsychopharmacol* 2012, 22:364–373, doi: 10.1016/j.euroneuro.2011.09.003

69. Liao CH, Chang CS, Wei WC, Chang SN, Liao CC, Lane HY et al. Schizophrenia patients at higher risk of diabetes, hypertension and hyperlipidemia: a population-based study. *Schizophr Res* 2011, 126:110–116, doi: 10.1016/j.schres.2010.12.007

70. Bushe C, Leonard B. Association between atypical antipsychotic agents and type 2 diabetes: review of prospective clinical data. *Br J Psychiatry Suppl* 2004, 47:S87–S93

71. Kessing LV, Thomsen AF, Mogensen UB, Andersen PK. Treatment with antipsychotics and the risk of diabetes in clinical practice. *Br J Psychiatry* 2010, 197:266–71, doi: 10.1192/bjp.bp.109.076935

72. Baker RA, Pikalov A, Tran QV, Kremenets T, Arani RB, Doraiswamy PM. Atypical antipsychotic drugs and diabetes mellitus in the US Food and Drug Administration Adverse Event database: a systematic Bayesian signal detection analysis. *Psychopharmacol Bull* 2009, 42:11–31

73. Megna JL, Schwartz TL, Siddiqui UA, Herrera Rojas M. Obesity in adults with serious and persistent mental illness: a review of postulated mechanisms and current interventions. *Ann Clin Psychiatry* 2011, 23:131–140

74. Sussman N, Ginsberg DL, Bikoff J. Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor- and imipramine-controlled trials. *J Clin Psychiatry* 2001, 62:256–260

75. Sachs GS, Guille C. Weight gain associated with use of psychotropic medications. *J Clin Psychiatry* 1999, 60(Suppl 21):16–19

76. Frank E, Kupfer DJ, Buhari A, McEachran AB, Grochocinski VJ. Imipramine and weight gain during the long-term treatment of recurrent depression. *J Affect Disord* 1992, 26:65–72

77. Bhattacharjee S, Bhattacharya R, Kelley GA, Sambamoorthi U. Antidepressant use and new-onset diabetes: a systematic review and meta-analysis. *Diabet Metabol Research Rev* 2013, 29:273–84, doi: 10.1002/dmrr.2393

78. Blumenthal SR, Castro VM, Clements CC, Rosenfield HR, Murphy SN, Fava M et al. An electronic health records study of long-term weight gain following antidepressant use. *JAMA Psychiatry*. 2014, 71:889–896, doi: 10.1001/jamapsychiatry.2014.414

79. Hasnain M, Vieweg WV, Hollett B. Weight gain and glucose dysregulation with second-generation antipsychotics and antidepressants: a review for primary care physicians. *Postgraduat Med* 2012, 124:154–167, doi: 10.3810/pgm.2012.07.2577

80. Brown LC, Majumdar SR, Johnson JA. Type of antidepressant therapy and risk of type 2 diabetes in people with depression. *Diab Research Clin Pract* 2008, 79:61–67, doi: 10.1016/j.diabres.2007.07.009

81. Andersohn F, Schade R, Suissa S, Garbe E. Long-term use of antidepressants for depressive disorders and the risk of diabetes mellitus. *Am J Psychiatry* 2009, 166:591–598, doi: 10.1176/appi.ajp.2008.08071065

82. Rubin RR, Ma Y, Marrero DG, Peyrot M, Barrett-Connor EL, Kahn SE et al. Elevated depression symptoms, antidepressant medicine use, and risk of developing diabetes during the diabetes prevention program. *Diabet Care* 2008, 31:420–426, doi: 10.2337/dc07-1827

83. Pylvanen V, Knip M, Pakarinen A, Kotila M, Turkka J, Isojarvi JI. Serum insulin and leptin levels in valproate-associated obesity. *Epilepsia* 2002, 43:514–517

84. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet* 2012, 379:721–728, doi: 10.1016/S0140–673661516-X

85. Verrotti A, la Torre R, Trotta D, Mohn A, Chiarelli F. Valproate-induced insulin resistance and obesity in children. *Hormon Research* 2009, 71:125–131, doi: 10.1159/000197868

86. Masuccio F, Verrotti A, Chiavaroli V, de Giorgis T, Giannini C, Chiarelli F et al. Weight gain and insulin resistance in children

treated with valproate: the influence of time. *J Child Neurol* 2010, 25:941–7, doi: 10.1177/0883073809349461

87. Luef GJ, Waldmann M, Sturm W, Naser A, Trinka E, Unterberger I et al. Valproate therapy and nonalcoholic fatty liver disease. *Ann Neurol* 2004, 55:729–32, doi: 10.1002/ana.20074

88. Bobo WV, Cooper WO, Stein CM, Olfson M, Graham D, Daugherty J et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. *JAMA Psychiatry* 2013, 70:1067–1075, doi: 10.1001/jamapsychiatry.2013.2053

89. Rubin DM, Kreider AR, Matone M, Huang YS, Feudtner C, Ross ME et al. Risk for incident diabetes mellitus following initiation of second-generation antipsychotics among Medicaid-enrolled youths. *JAMA Pediatrics*. 2015, 169:e150285, doi: 10.1001/jama-pediatrics.2015.0285

90. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol* 2011, 8:114–126, doi: 10.1038/nrendo.2011.156

91. McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH. The effect of antidepressants on lipid homeostasis: a cardiac safety concern? *Expert Opin Drug Saf* 2006, 5:523–537, doi: 10.1517/14740338.5.4.523

92. McIntyre RS, McElroy SL, Eudicone JM, Forbes RA, Carlson BX, Baker RA. A 52-week, double-blind evaluation of the metabolic effects of aripiprazole and lithium in bipolar I disorder. *The primary care companion for CNS disorders*. 2011:13, doi: 10.4088/PCC.11m01182

93. Chang HH, Yang YK, Gean PW, Huang HC, Chen PS, Lu RB. The role of valproate in metabolic disturbances in bipolar disorder patients. *J Affect Disord* 2010, 124:319–323, doi: 10.1016/j.jad.2009.12.011

94. Correll CU. From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. *Eur Psychiatry* 2010, 25(Suppl 2):S12–S21, doi: 10.1016/S0924–933871701–6

95. Stahl SM, Grady MM, Moret C, Briley M. SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *CNS Spectrums* 2005, 10:732–747

96. Watanabe N, Omori IM, Nakagawa A, Cipriani A, Barbui C, McGuire H et al. Safety reporting and adverse-event profile of mirtazapine described in randomized controlled trials in comparison with other classes of antidepressants in the acute-phase treatment of adults with depression: systematic review and meta-analysis. *CNS Drugs* 2010, 24:35–53, doi: 10.2165/11319480-000000000-00000

97. Guest PC, Wang L, Harris LW, Burling K, Levin Y, Ernst A et al. Increased levels of circulating insulin-related peptides in first-onset, antipsychotic naive schizophrenia patients. *Mol Psychiatry* 2010, 15:118–119, doi: 10.1038/mp.2009.81

98. Harris LW, Guest PC, Wayland MT, Umrania Y, Krishnamurthy D, Rahmoune H et al. Schizophrenia: metabolic aspects of aetiology, diagnosis and future treatment strategies. *Psychoneuroendocrinology* 2013, 38:752–766, doi: 10.1016/j.psyneuen.2012.09.009

99. Sarnyai Z, Jashar C, Olivier B. Modeling combined schizophrenia-related behavioral and metabolic phenotypes in rodents. *Behav Brain Res* 2015, 276:130–142, doi: 10.1016/j.bbr.2014.04.016

100. Cohen D, De Hert M. Endogenic and iatrogenic diabetes mellitus in drug-naive schizophrenia: the role of olanzapine and its place in the psychopharmacological treatment algorithm. *Neuropsychopharmacology* 2011, 36:2368–2369, doi: 10.1038/npp.2011.94

101. Song X, Fan X, Song X, Zhang J, Zhang W, Li X et al. Elevated levels of adiponectin and other cytokines in drug naive, first episode schizophrenia patients with normal weight. *Schizophr Res* 2013, 150:269–273, doi: 10.1016/j.schres.2013.07.044

102. Becker KG, Barnes KC, Bright TJ, Wang SA. The genetic association database. *Nat Genet* 2004, 36:431–432, doi: 10.1038/ng0504–431

103. Gasperoni TL, Ekelund J, Huttunen M, Palmer CG, Tuulio-Henriksson A, Lonnqvist J et al. Genetic linkage and association between chromosome 1q and working memory function in schizophrenia. American journal of medical genetics Part B. *Neuropsychiatr Genet* 2003, 116B:8–16, doi: 10.1002/ajmg.b.10757

104. Zeggini E, Damcott CM, Hanson RL, Karim MA, Rayner NW, Groves CJ et al. Variation within the gene encoding the upstream stimulatory factor 1 does not influence susceptibility to type 2 diabetes in samples from populations with replicated evidence of linkage to chromosome 1q. *Diabetes* 2006, 55:2541–8, doi: 10.2337/db06–0088

105. Wolford JK, Hanson RL, Kobes S, Bogardus C, Prochazka M. Analysis of linkage disequilibrium between polymorphisms in the KCNJ9 gene with type 2 diabetes mellitus in Pima Indians. *Mol Genet Metab* 2001, 73:97–103, doi: 10.1006/mgme.2001.3167

106. Lin PI, Shuldiner AR. Rethinking the genetic basis for comorbidity of schizophrenia and type 2 diabetes. *Schizophr Res* 2010, 123:234–243, doi: 10.1016/j.schres.2010.08.022

107. Alkelai A, Greenbaum L, Lupoli S, Kohn Y, Sarner-Kanyas K, Ben-Asher E et al. Association of the type 2 diabetes mellitus susceptibility gene, TCF7L2, with schizophrenia in an Arab-Israeli family sample. *PloS One* 2012, 7:e29228, doi: 10.1371/journal.pone.0029228

108. Hansen T, Ingason A, Djurovic S, Melle I, Fenger M, Gustafsson O et al. At-risk variant in TCF7L2 for type II diabetes increases risk of schizophrenia. *Biol Psychiatry* 2011, 70:59–63, doi: 10.1016/j.biopsych.2011.01.031

109. Hindorff LA, Sethupathy P, Junkins HA, Ramos EM, Mehta JP, Collins FS et al. Potential etiologic and functional implications of genome-wide association loci for human diseases and traits. *Proceed Nat Acadf Sci Unit Stat Am* 2009, 106:9362–9367, doi: 10.1073/pnas.0903103106

110. Kajio Y, Kondo K, Saito T, Iwayama Y, Aleksic B, Yamada K et al. Genetic association study between the detected risk variants based upon type II diabetes GWAS and psychotic disorders in the Japanese population. *J Hum Genet* 2014, 59:54–56, doi: 10.1038/jhg.2013.116

111. Liu Y, Li Z, Zhang M, Deng Y, Yi Z, Shi T. Exploring the pathogenetic association between schizophrenia and type 2 diabetes mellitus diseases based on pathway analysis. *BMC Med Genom* 2013, 6(Suppl 1):S17, doi: 10.1186/1755–8794-6-S1-S17

112. Mausdley H. *The Pathology of Mind*. D. Appleton and Company, NY: New York, 1897

Corresponding author: V. Mamakou, Medical School, National and Kapodistrian University of Athens, 75 M. Assias street, GR-115 27 Athens, Greece, e-mail: vmamakou@med.uoa.gr