Metaboličke nuspojave novijih antipsihotika

Metabolic side-effects of novel antipsychotic drugs

Ana Kovak-Mufić[1], Dalibor Karlović[1], Marko Martinac[2], Darko Marčinko[3], Katica Letinić[1], Branka Vidrih[1]

[1] Klinika za psihijatriju, Klinička bolnica „Sestre milosrdnice", Zagreb, Hrvatska

[1] Department of Psychiatry, Sestre milosrdnice University Hospital, Zagreb, Croatia

[2] Centar za prevenciju i izvanvanbolničko liječenje ovisnosti, Mostar

[2] Center for Prevention and Treatment of Addictions, Mostar, Bosnia & Herzegovina

[3] Klinika za psihijatriju, Klinički bolnički centar Zagreb, Zagreb, Hrvatska

[3] Department of Psychiatry, KBC Zagreb, Zagreb, Croatia

Sažetak

Prvi opisani slučajevi metaboličkih nuspojava antipsihotika potječu još od vremena kada se ti lijekovi uvode u kliničku upotrebu, tj. sredinom pedesetih godina prošlog stoljeća. Pokazalo se, međutim, da se metaboličke nuspojave ne javljaju samo kod primjene konvencionalnih antipsihotika, poput klorpromazina. Danas smo suočeni sa sličnim problemima kod primjene novijih, takozvanih atipičnih antipsihotika. Uvođenje atipičnih antipsihotika u terapiju bitno je unaprijedilo liječenje bolesnika sa shizofrenijom i ostalim psihotičnim poremećajima. Glavna prednost ovih lijekova u odnosu na konvencionalne antipsihotike je manja učestalost ekstrapiramidnih nuspojava, kao i hiperprolaktinemije, te sveukupno bolja podnošljivost. Ipak, neki od atipičnih antipsihotika povezuju se s porastom tjelesne težine, pojavom šećerne bolesti i porastom vrijednosti kolesterola i triglicerida.

Ovaj se pregled bavi razlikama u djelovanju pojedinih atipičnih antipsihotika na homeostazu glukoze i inzulina te metabolizam lipida, kao i pitanjem na koji način racionalno primjenjivati antipsihotike kod kojih se javljaju metaboličke nuspojave. Odnosno, daju se preporuke, po prvi put u Hrvatskoj, za svakodnevni klinički rad o tome kako nadzirati metabolički status bolesnika liječenih novijim antipsihoticima.

Ključne riječi: metabolički sindrom, nuspojave, antipsihotici, metabolizam lipida, metabolizam glukoze

Abstract

First descriptions of metabolic side-effects of antipsychotic drugs date back to the 1950s when these drugs were introduced. In the meantime, metabolic side-effects have been shown to occur not only during therapy including conventional antipsychotics like chlorpromazine. Presently, similar problems are encountered with application of the novel, so-called atypical antipsychotics. Introduction of atypical antipsychotics in therapy has substantially promoted the treatment of patients with schizophrenia and other psychotic disorders. Major advantage of these drugs in comparison to conventional antipsychotics is lower frequency of extrapyramidal side-effects and hyperprolactinemia, and generally better tolerance. Still, some atipical antipsychotics are associated to body weight gain, occurrence of diabetes, and elevated cholesterol and triglyceride concentrations.

This review addresses differences in effect of certain atypical antipsychotics on glucose and insulin homeostasis and lipid metabolism, as well as the question of the rational method of applying antipsychotics that are accompanied by metabolic side-effects. For the first time in Croatia, this article provides recommendations for routine clinical practice, i.e. on the monitoring of metabolic status of patients treated by novel antipsychotics.

Key words: metabolic syndrome, side-effects, antipsychotics, lipid metabolism, glucose metabolism

Pristiglo: 15. siječnja 2007. *Received: January 15, 2007*

Prihvaćeno: 20. lipnja 2007. *Accepted: June 20, 2007*

Uvod

Prvi opisani slučajevi metaboličkih nuspojava antipsihotika potječu još iz 1956. godine. Tada su, četiri godine nakon uvođenja prvog antipsihotika klorpromazina u terapiju, objavljeni podatci o pojavi hiperglikemije i glukozurije kod prethodno euglikemičnih bolesnika koji su uzimali klorpromazin. U isto vrijeme opisani su i slučajevi o sla-

Introduction

The first described cases of metabolic side-effects of antipsychotics date back to 1956. That was the time when, four years after introduction of the first antipsychotic chlorpromazine in therapy, data were published on the occurrence of hyperglycemia and glucosuria in previously euglycemic patients who were administered chlorpro-

bijoj kontroli glikemije u dijabetičara koji su uzimali klorpromazin. Nakon isključivanja klorpromazina u opisanim slučajevima došlo je do normaliziranja glikemije, odnosno do uspostavljanja kontrole šećerne bolesti kakva je bila i prije uzimanja antipsihotika (1,2).

Pokazalo se, međutim, da se metaboličke nuspojave ne javljaju samo kod primjene konvencionalnih antipsihotika poput klorpromazina. Danas smo, naime, suočeni sa sličnim problemima kod primjene novijih, takozvanih atipičnih antipsihotika. Uvođenje atipičnih antipsihotika u terapiju bitno je unaprijedilo liječenje bolesnika sa shizofrenijom i ostalim psihotičnim poremećajima. Glavna prednost ovih lijekova u odnosu na konvencionalne antipsihotike je manja učestalost ekstrapiramidnih nuspojava, kao i hiperprolaktinemije, te sveukupno bolja podnošljivost. Ipak, neki od atipičnih antipsihotika povezuju se s porastom tjelesne težine, pojavom šećerne bolesti i porastom koncentracije kolesterola i triglicerida (Tablica 1).

Ovaj se pregled bavi razlikama u djelovanju pojedinih atipičnih antipsihotika na homeostazu glukoze i inzulina te metabolizam lipida, kao i pitanjem na koji način racionalno primjenjivati antipsihotike kod kojih se javljaju metaboličke nuspojave.

Utjecaj atipičnih antipsihotika na homeostazu glukoze i inzulina

Najveći broj objavljenih kliničkih studija koje se bave homeostazom glukoze i inzulina odnose se na klozapin, olanzapin i risperidon, dok je broj studija o metaboličkim

mazine. There were also concurrent descriptions of cases of impaired glycemic control in diabetics on chlorpromazine therapy. Upon discontinued administration of chlorpromazine, normalization of glycemia was achieved as well as diabetes control at the levels prior to antipsychotic therapy (1,2).

Metabolic side-effects have, however, been shown to accompany not only the administration of conventional antipsychotics like chlorpromazine. Actually, we presently face similar problems during introduction of the novel, so-called atypical antipsychotics. Introduction of atypical antipsychotics in therapy has significantly promoted the treatment of patients affected by schizophrenia and other psychotic disorders. Compared to conventional antipsychotics, the major advantage of these drugs is lower frequency of extrapyramidal side-effects and of hyperprolactinemia, and better overall tolerance. Still, some of atypical antipsychotics have been associated with body weight gain, occurrence of diabetes, and increase in cholesterol and triglyceride levels (Table 1).

This review addresses differences in the effect of certain atypical antipsychotics on glucose and insulin homestasis and lipid metabolism, as well as the issue of the method of rational administration of antipsychotics accompanied by metabolic side-effects.

Effect of atypical antipsychotics on glucose and insulin homeostasis

The highest number of published clinical studies dealing with glucose and insulin homeostasis refer to clozapine,

Tablica 1. Pregled potencijala pojedinih antipsihotika za razvoj poremećaja metabolizma lipoproteina

Table 1. Review of the potential of some antipsychotics for the development of lipoprotein metabolism disorder

Antipsychotic (generic name)	Potential for lipid disorder development	Daily therapeutic antipsychotic doses (mg)
Haloperidol	+	6-20
Flufenazine	+	1-20
Promazine	+	50-800
Levomepromazine	+	100-400
Zuclopentixol	-/+	10-75
Sulpiride	+	400-1200
Clozapine*	+++	50-500
Olanzapine*	+++	5-20
Ziprasidone*	-	80-160
Quetiapine*	+	300-600
Risperidone*	+	1-6
Sertindole*	++	12-20
Aripiprazole*	+	10-30

*A new generation antipsychotic

nuspojavama drugih atipičnih antipsihotika relativno mali.

Kod tumačenja rezultata tih studija potrebno je uzeti u obzir da, osim uzimanja atipičnih antipsihotika, kod bolesnika koji se liječe nekim od ovih lijekova još najmanje sedam faktora također može pridonijeti pojavi tkivne rezistencije na inzulin i posljedično povećati rizik od šećerne bolesti: starija dob, šećerna bolest tipa II u obitelji, etnička pripadnost, pretilost, pušenje, manjak tjelesne aktivnosti i uzimanje drugih dijabetogenih lijekova (3-5). Komparativne studije su pokazale da klozapin i olanzapin povećavaju rizik od pojave nepodnošenja glukoze i šećerne bolesti, dok risperidon nema takav učinak.

Što se tiče kvetiapina, objavljene su samo dvije komparativne studije koje ne daju dovoljno jasne rezultate. Niti jedna komparativna studija nije objavljena u vezi s amisulpridom, zotepinom, ziprasidonom i aripiprazolom.

Klozapin

Melkersson i suradnici su mjerili koncentraciju inzulina natašte, te koncentraciju klozapina ili klasičnih antipsihotika. Studija je pokazala da je razina inzulina u pozitivnoj korelaciji s koncentracijom klozapina, dok između razine inzulina i koncentracije klasičnih antipsihotika nema korelacije. Prema tim rezultatima moguće je zaključiti da klozapin izravno utječe na lučenje inzulina iz pankreasa (6).

Studija koju su proveli Chae i Kang uspoređivala je utjecaj klozapina i klasičnog antipsihotika haloperidola na metabolizam glukoze putem oralnog testa podnošenja glukoze (OGTT). Nakon 8 tjedana terapije, 35% bolesnika koji su uzimali klozapin imalo je poremećeno podnošenje glukoze, dok među bolesnicima koji su uzimali haloperidol nije bilo takvog poremećaja (7).

Henderson i suradnici su tijekom pet godina pratili 82 bolesnika sa shizofrenijom ili shizoafektivnom psihozom. 37% bolesnika je tijekom petogodišnjeg praćenja razvilo šećernu bolest. Radilo se o bolesnicima prosječne dobi od 36 godina i indeksom tjelesne mase prosječno 27. Rezultati studije pokazali su da je razvoj šećerne bolesti korelirao s dobi bolesnika, dok s tjelesnom težinom, promjenama u tjelesnoj težini i promjenama dnevnih doza klozapina nije bilo korelacije. Obiteljska anamneza bila je pozitivna na šećernu bolest tipa II samo kod dva bolesnika (8). Još uvijek nije razjašnjeno utječu li tip i težina psihičkog poremećaja na rizik od razvoja šećerne bolesti u bolesnika koji uzimaju klozapin (9).

Olanzapin

U studiji objavljenoj 2000. godine hiperinzulinemija je utvrđena kod 71% bolesnika sa shizofrenijom ili srodnim oblicima psihoza koji su liječeni olanzapinom u trajanju od prosječno 6 mjeseci. Kod troje od tih bolesnika utvrđena je i hiperglikemija, što je upućivalo na razvoj šećerne bolesti (10).

olanzapine and risperidone, with relatively few studies of metabolic side-effects of other atypical antipsychotics. When interpreting results of these studies, it should be taken into account that, in addition to administration of any of the above atypical antipsychotics to patients, there are at least other seven factors that may also contribute to the occurrence of tissue resistance to insulin and thus increase the risk for diabetes: old age, family history of type 2 diabetes, ethnic origin, obesity, smoking, lack of physical activity, and therapy with other diabetogenic drugs (3-5). Comparative studies have demonstrated that clozapine and olanzapine elevate the risk for occurrence of glucose intolerance and diabetes, while risperidone does not have such effect.

With regard to quetiapine, only two comparative studies have been published and they do not provide sufficiently clear results. No comparative study has been published to include amilsulpride**,** zotepine**,** ziprasidone, and aripiprazole.

Clozapine

Melkersson et al. have measured insuline concentration after overnight fasting, and the concentration of clozapine and other classical antipsychotics. The study showed the insulin level to be positively correlated to clozapine concentration, while no correlation was observed between insulin level and the concentration of classical antipsychotics. Based on these results, it may be concluded that clozapine directly affects pancreatic insulin secretion (6).

The study performed by Chae and Kang compared the effect of clozapine and the classical antipsychotic haloperidol on glucose metabolism through oral glucose tolerance test (OGTT). Following 8 weeks of therapy, 35% patients who were administered clozapine had impaired glucose tolerance, while no such impairment was observed in patients on haloperidol (7).

Henderson et al. included 82 patients affected by schizophrenia or schizoaffective psychosis in a 5-year follow-up. Diabetes developed in 37% of patients during the 5-year monitoring. Their mean age was 36 years and mean body mass index was 27. Results of the study showed that diabetes development correlated to patients' age, while no correlation was recorded for body weight, changes in body weight, and changes in daily clozapine doses. Family history was positive for type 2 diabetes in only two patients (8). It has not been elucidated yet if the type and severity of mental disorder affects the risk for diabetes development in patients on clozapine (9).

Olanzapine

In a study published in year 2000, hyperinsulinemia was established in 71% of patients with schizophrenia or related types of psychoses who were on olanzepine therapy for 6 months on average. Hyperglycemia was also confir-

Druga je studija pokazala da u razdoblju od 25 mjeseci liječenja olanzapinom 44% bolesnika razvija hiperinzulinemiju sa ili bez hiperglikemije (11).
Prospektivna studija u trajanju od 14 tjedana pokazala je da 11% bolesnika liječenih olanzapinom ima intermitentnu ili trajno prisutnu hiperglikemiju. Svi uključeni bolesnici prethodno su slabo reagirali na terapiju drugim antipsihoticima (12).

Kvetiapin

Otvorena, nerandomizirana retrospektivna studija ispitivala je promjene tjelesne težine i dijabetičkog statusa u 65 bolesnika koji su najprije uzimali klozapin kao monoterapiju kroz šest mjeseci, a zatim su deset mjeseci primali kombiniranu terapiju klozapinom i kvetiapinom. Rezultat je bilo značajno smanjenje tjelesne težine kod svih bolesnika i bolja kontrola glikemije u 20% bolesnika koji su prethodno razvili šećernu bolest na monoterapiju klozapinom (13). Ti rezultati ukazuju da smanjenje doze klozapina dovodi do smanjenja tjelesne težine, izazvane ovim lijekom, kao i na to da kvetiapin nema bitnog učinka na promjenu tjelesne težine i metabolizam glukoze (13).

Risperidon

Osim nekoliko komparativnih studija, objavljena su samo dva prikaza bolesnika na risperidonu koji su pokazali da ovaj lijek nije doveo ni do kakvih komplikacija vezanih uz regulaciju glikemije u psihotičnih bolesnika s šećernom bolesti u komorbiditetu (14,15).
Za sada u literaturi nisu dostupni podatci o nuspojavama amisulprida, aripiprazola, ziprasidona i zotepina koje se odnose na poremećaj homeostaze glukoze i inzulina (9).

Prikazi bolesnika

U zadnjih petnaestak godina objavljeni su brojni prikazi slučajeva bolesnika koji su nakon uvođenja atipičnih antipsihotika u terapiju razvili šećernu bolest, dijabetičku ketoacidozu, hiperosmolarnu dijabetičku komu ili je dolazilo do poremećaja kontrole glikemije kod preegzistirajuće šećerne bolesti. Podatci variraju ovisno o izvoru, no najveći broj ovakvih prikaza vezan je uz olanzapin i klozapin, zatim za risperidon, svega je nekoliko prikaza objavljeno za kvetiapin, jedan za ziprasidon, dok za zotepin, aripiprazol i amisulprid nema objavljenih prikaza slučaja (9). Objavljeni su i slučajevi smrti bolesnika zbog razvoja hiperosmolarne dijabetičke kome, odnosno zbog metaboličke acidoze ili ketoze, i to kod terapije olanzapinom i klozapinom (16-20). Koller i sur. prikazali su slučajeve bolesnika s novodijagnosticiranom šećernom bolesti: 242 bolesnika na terapiji klozapinom, 225 na terapiji olanzapinom i 78 bolesnika na terapiji risperidonom. Broj bolesnika koji su razvili metaboličku acidozu ili ketozu bio je sukladno tome 80, 100 i 26 (21-23). Autori su slučajeve smrti tijekom hiperglikemijskih epizoda prijavili kod 25 bolesnika na klomed in three of these patients, and indicated the onset of diabetes (10).
Another study showed the development of hyperinsulinemia with or without hyperglycemia in 44% of patients who were on olanzepine therapy for the period of 25 months (11).
A prospective study involving a 14-week period demonstrated the development of intermittent or permanently present hyperglycemia in 11% of olanzepine-treated patients. All included patients formerly reacted poorly to therapy by other antipsychotics (12).

Quetiapine

An open, non-randomized retrospective study investigated changes in body weight and diabetic status of 65 patients who were on clozapine as monotherapy for 6 months, and then were administered combined clozapine and quetiapine therapy for ten months. The result was substantial reduction in body weight in all patients and better control of glycemia in 20% of patients who previously developed diabetes while on clozapine monotherapy (13). These results indicate that reduction in clozapine dose leads to reduction in body weight that is caused by this drug, and that quetiapine has no significant effect on body weight change and glucose metabolism (13).

Risperidone

Apart from several comparative studies, only two case reports of patients on risperidone have been published which showed that this drug did not lead to any complications related to regulation of glycemia in psychotic patients with comorbid diabetes (14,15).
Presently, literature provides no data on side-effects of amilsulpride, aripiprazole, ziprasidone and zotepine that are related to disturbance in glucose and insulin homeostasis (9).

Case reports

During past 15 years, numerous case reports were published on patients who developed diabetes, diabetic ketoacidosis, and hyperosmolar diabetic coma after introduction of atypical antipsychotics in therapy, or who experienced impaired glycemic control in preexisting diabetes. Data vary depending on the source, yet most of these studies are related to olanzapine and clozapine, then to risperidone, with only several studies published for quetiapine and one for ziprasidone, while no case reports have been published for zotepine, aripiprazole and amilsulpride (9). There have also been reports of patient death due to hyperosmolar diabetic coma or metabolic acidosis or ketosis during olanzapine and clozapine therapy (16-20). Koller et al. presented reports on patients with newly diagnosed diabetes, i.e. 242 patients on clozapine therapy, 225 on olanzapine therapy, and 78 patients on

zapinu, 25 bolesnika na olanzapinu i 4 bolesnika na risperidonu (21-23).
Ananth i sur. su objavili pregled koji pokazuje da je kod 71% bolesnika, kod kojih je terapija atipičnim antipsihoticima izazvala pojavu šećerne bolesti ili dijabetičke ketoacidoze, došlo do oporavka nakon prekida antipsihotične terapije (24). Iz toga zaključujemo da se metaboličke nuspojave povlače nakon prekida terapije kod većine, no ipak ne kod svih bolesnika.

Mogući mehanizmi kojima atipični antipsihotici izazivaju inzulinsku rezistenciju i šećernu bolest

Faktori koji mogu uzrokovati tkivnu rezistenciju na inzulin su: starenje, šećerna bolest tipa 2 u obitelji, etnička pripadnost, pretilost, pušenje i manjak tjelesne aktivnosti (3,4).
Atipični antipsihotici uzrokuju porast tjelesne težine (25-29), umiruju bolesnike i time posredno djeluju na smanjenje tjelesne aktivnosti, te se smatra da na ovaj način pojačavaju inzulinsku rezistenciju, što rezultira hiperlipidemijom i povećanjem rizika za razvoj šećerne bolesti tipa 2 i kardiovaskularnih bolesti (30,31).
Sljedeći mehanizam kojim atipični antipsihotici povećavaju rizik od nastanka šećerne bolesti je izravan utjecaj na ravnotežu glukoze i inzulina - klozapin i olanzapin uzrokuju hiperinzulinemiju i hiperlipidemiju (6,10,11,32). Hiperinzulinemija i hiperlipidemija same povećavaju inzulinsku rezistenciju (31) i time rizik od razvoja šećerne bolesti tipa 2.
Kad je riječ o šećernoj bolesti induciranoj lijekovima, pokazalo se da je dob važan faktor rizika za njezin razvoj (8), dok pušenje i manjak tjelesne aktivnosti kod ovog tipa šećerne bolesti najvjerojatnije ne predstavljaju značajan faktor rizika.
Za razliku od šećerne bolesti tipa 2, prisutnost bolesti u obitelji i povećana tjelesna težina ne predstavljaju značajnije faktore rizika za razvoj šećerne bolesti inducirane lijekovima (8,33).

Moguća povezanost shizofrenije i šećerne bolesti

Prevalencija šećerne bolesti tipa 2 veća je u bolesnika koji boluju od shizofrenije, nego u općoj populaciji (34). Do danas nije istraženo zbog čega je tako.
Mogući razlog je što se važni faktori rizika za razvoj šećerne bolesti tipa 2, kao što su debljina, pušenje i manjak tjelesne aktivnosti, puno češće nalaze u shizofrenih bolesnika nego u općoj populaciji (35-37).
Postoje podatci o tome da je shizofrenija kao bolest sama po sebi povezana s poremećenim podnošenjem glukoze i šećernom bolesti, no nije poznato kakav rizik za razvoj šećerne bolesti tipa 2 ili šećerne bolesti inducirane lijekovima predstavlja tip psihotičnog poremećaja i težina bolesti (9).

risperidone therapy. The numbers of patients who developed metabolic acidosis or ketosis were 80, 100, and 26, respectively (21-23). Authors reported cases of death during hyperglycemic episodes for 25 patients on clozapine, 25 patients on olanzapine, and 4 patients on risperidone (21-23).
Ananth et al. published a review demonstrating recovery after therapy discontinuation in 71% of patients with diabetes or diabetic ketoacidosis caused by therapy with atypical antipsychotics (24). Based on these observations, it may be concluded that metabolic side-effects withdraw after therapy discontinuation in most, yet not in all patients.

Possible mechanisms by which atypical antipsychotics induce insulin resistance and diabetes

The factors that may cause tissue resistance to insulin are aging, family history of type 2 diabetes, ethnic origin, obesity, smoking, and lack of physical activity (3,4).
Atypical antipsychotics cause body weight gain (25-29), sedate patients and thereby act indirectly to reduce body weight, and are thus considered to enhance insulin resistance which results in hyperlipidemia and increased risk for the development of type 2 diabetes and cardiovascular diseases (30,31).
Another mechanism by which atypical antipsychotics enhance diabetes risk is a direct effect on glucose and insulin balance; actually, clozapine and olanzapine induce hyperinsulinemia and hyperlipidemia (6,10,11,32). Hyperinsulinemia and hyperlipidemia themselves augment insulin resistance (31) and thereby also the risk for the development of type 2 diabetes.
With regard to drug-induced diabetes, age was shown to be a risk factor for its development (8), while smoking and lack of physical activity most probably do not represent significant risk factors for this type of diabetes.
Unlike in type 2 diabetes, family history of the disease and body weight gain are not significant risk factors for the development of drug-induced diabetes (8,33).

Possible correlation of schizophrenia and diabetes

The prevalence of type 2 diabetes is higher in patients affected by schizophrenia than in the general population (34). No research has been done so far to account for this difference.
Possible reason is that important risk factors for the development of type 2 diabetes, like obesity, smoking and lack of physical activity, are more frequently observed in schizophrenic patients than in the general population (35-37).
Data are available to demonstrate that schizophrenia itself as a disease is related to impaired glucose tolerance and diabetes, yet the nature of the risk that a type or severity

Atipični antipsihotici i serumski lipidi

Studije koje se bave utjecajem atipičnih antipsihotika na serumske lipide su relativno malobrojne. U nastavku navodimo istraživanja prema antipsihotiku (klozapinu, olanzapinu, risperidonu, kvetiapinu, ziprazidonu i aripiprazolu).

Klozapin

Prema dosad objavljenim podatcima, klozapin utječe na povišenje koncentracije triglicerida. Analiza podataka iz *Iowa Medicaid Programa* (38) uspoređivala je pojavu hiperlipidemije u bolesnika liječenih klozapinom i bolesnika liječenih konvencionalnim antipsihoticima. Ukupno gledajući, razlika u pojavnosti hiperlipidemije između dvije skupine bolesnika nije bila statistički značajna. Međutim, nakon raspodjele bolesnika prema dobnim skupinama, pokazalo se da je pojavnost hiperlipidemije kod bolesnika liječenih klozapinom, u dobi između 20 i 34 godine, bitno veća u odnosu na istu dobnu skupinu na terapiji konvencionalnim antipsihoticima.

Druga je studija pokazala učinak klozapina na promjenu koncentracija serumskih lipida tijekom 12 mjeseci praćenja (39). Na kraju studije broj bolesnika s hipertrigliceridemijom bio je značajno veći (19 bolesnika) u odnosu na početak studije (7 bolesnika). Također je kod tih bolesnika došlo i do bitnog povećanja tjelesne težine.

Utjecaj klozapina na koncentraciju kolesterola još uvijek nije dovoljno razjašnjen. Naime, od svih do sad objavljenih studija na ovu temu, samo dvije navode povišenje kolesterola kod bolesnika liječenih klozapinom (39,40), dok ostale ne navode bitan utjecaj klozapina na kolesterol (41-43).

Risperidon

Rezultati dobiveni analizom podataka o više od 18.000 bolesnika iz britanske zdravstvene baze podataka (UK GPRD) pokazali su da risperidon nije u značajnijoj mjeri povezan s hiperlipidemijom (44).

Retrospektivna studija, koju je proveo Meyer (45), ispitivala je tijekom perioda od 12 mjeseci promjene u serumskim koncentracijama kolesterola i triglicerida u bolesnika koji su uzimali risperidon. Rezultati su pokazali da taj antipsihotik ne utječe u značajnoj mjeri na serumske koncentracije kolesterola, dok istovremeno uzrokuje porast koncentracije triglicerida. Risperidon je također povezan s porastom tjelesne težine, koja pozitivno korelira s koncentracijom serumskih lipida.

Ostale studije koje se mogu naći u literaturi također potvrđuju da risperidon nema bitan učinak na promjene koncentracije serumskog kolesterola, dok su podatci o utjecaju na vrijednosti triglicerida nedovoljno dosljedni. Naime, samo je jedna studija pokazala porast koncentracije triglicerida koji je bio statistički značajan (45).

of a psychotic disorder pose for the development of type 2- or drug-induced diabetes is unknown (9).

Atypical antipsychotics and serum lipids

The studies dealing with the effect of atypical antipsychotics on serum lipids are relatively few. Studies are described in the following paragraphs according to the antipsychotics involved (clozapine, olanzapine, risperidone, quetiapine, ziprasidone, aripiprasole).

Clozapine

Based on the hitherto published data, clozapine induces an increase in the level of triglycerides. Analysis of data from the Iowa Medicaid Program (38) compared the occurrence of hyperlipidemia in clozapine-treated patients and those treated by conventional antipsychotics. Overall, the difference in hyperlipidemia incidence between the two patient groups was not statistically significant. However, after patient distribution according to age groups, the incidence of hyperlipidemia was shown in clozapine-treated patients aged 20-34 years to be substantially higher compared to the same age group on therapy with conventional antipsychotics.

Another study showed the effect of clozapine on the change in serum lipid level during a 12-month follow-up period (39). At the end of the study, the number of patients with hypertriglyceridemia was significantly higher (19 patients) in relation to the study onset (7 patients). Also, a substantial body weight gain was observed in hypertriglyceridemic patients.

Effect of clozapine on cholesterol level has not yet been sufficiently elucidated. Actually, from all studies dealing with this topic so far, elevated cholesterol levels were observed in clozapine-treated patients in only two studies (39,40), while other studies stated no significant clozapine effect on cholesterol (41,42,43).

Risperidone

The results obtained by analyzing data on more than 18.000 patients from UK General Practice Research Database (UK GPRD) showed that risperidone was to no significant extent associated with hyperlipidemia (44).

A retrospective study conducted by Meyer (45) examined changes in serum levels of cholesterol and triglycerides in patients on risperidone during a 12-month period. The results demonstrated that this antipsychotic did not have any significant effect on serum cholesterol concentrations but caused concurrent increase in triglyceride level. Risperidone was also associated with body weight gain which positively correlates with serum lipid levels.

Other studies that may be found in the literature also confirm that risperidone has no substantial effect on changes in serum cholesterol levels, while data on its effect on triglyceride concentrations are insufficiently consistent. In

Olanzapin

Analiza podataka iz britanske baze UK GPRD pokazala je da je primjena olanzapina povezana s povećanim rizikom od razvoja hiperlipidemije (44).
Sličan je rezultat i Meyerove retrospektivne studije (45) koja je pokazala značajan porast koncentracije i triglicerida i kolesterola kod bolesnika koji su uzimali olanzapin. Taj je lijek uzrokovao i porast tjelesne težine što, međutim, nije bilo u bitnoj korelacije s promjenama vrijednosti kolesterola i triglicerida. Zanimljivo je i opažanje da su najviše koncentracije triglicerida izmjerene unutar prve godine uzimanja lijeka.
Nekoliko drugih studija također potvrđuje značajan utjecaj olanzapina na povišenje koncentracije serumskih lipida i to triglicerida (46-49), ukupnog kolesterola (47,18) i LDL-kolesterola (18,50), a na smanjenje HDL-kolesterola (51).

Kvetiapin

Studije koje se bave utjecajem kvetiapina na serumske lipide su relativno malobrojne, a rezultati tih studija nisu dosljedni.
Mala studija koju su proveli Wirshing i sur. (41) pokazala je da terapija kvetiapinom povoljno djeluje na koncentracije triglicerida i LDL-kolesterola tako što ih snižava, dok se koncentracije HDL-kolesterola tek minimalno mijenjaju.
Suprotno tome, prikupljeni laboratorijski rezultati iz jedne od kliničkih studija koje se bave kvetiapinom pokazali su povećanje koncentracije ukupnog kolesterola i triglicerida.

Ziprasidon

Rezultati studije, koja je proučavala učinak ziprasidona na serumske lipide kod bolesnika s mentalnom retardacijom i poremećajima ponašanja, pokazali su povoljno djelovanje ziprasidona na snižavanje koncentracije kolesterola i triglicerida (52).
Pet kratkotrajnih kliničkih studija, koje su proučavale učinke ziprasidona kod bolesnika sa shizofrenijom, pokazalo je da je uz terapiju ziprasidonom došlo do značajnog sniženja koncentracije kolesterola i triglicerida (53).
Za sada je broj studija i podataka o utjecaju ziprasidona na serumske lipide nedovoljan da bi se mogli izvući relevantni zaključci. Naime, najveći broj podataka govori u prilog tome da ziprasidon nema značajnijeg utjecaja na koncentracije kolesterola i triglicerida, odnosno, kao što je navedeno, da može povoljno djelovati na vrijednosti lipida kod bolesnika kod kojih su prethodno ove vrijednosti bile povišene.

Aripiprazol

Podatci koji su za sada dostupni pokazuju da bi aripiprazol mogao imati povoljan učinak na koncentracije serumskih lipida. Naime, pokazalo se da tijekom terapije aripiprazolom u fact, only one study reported a rise in triglyceride levels that was not statistically significant (45).

Olanzapine

Analysis of the data from the UK General Practice Research Database, UK GPRD**,** demonstrated that olanzapine administration was associated with elevated risk for the development of hyperlipidemia (44).
A similar result was also obtained in Meyer's retrospective study (45) which demonstrated a significant increase in the levels of both triglycerides and cholesterol of olanzapine-treated patients. This drug also caused body weight gain which was, however, not substantially correlated to changes in cholesterol and triglyceride concentrations. It is also interesting that highest triglyceride levels were registered during the first year of olanzapine administration.
Several other studies also confirmed the significant effect of olanzapine on the rise in the serum levels of lipids, i.e. triglycerides (46-49), total cholesterol (47,18) and LDL-cholestol (18,50), and on HDL-cholesterol decline (51).

Quetiapine

The studies investigating quetiapine effect on serum lipids have been relatively scarce and with rather inconsistent results.
A small-scale study conducted by Wirshing et al. (41) showed that quetiapine therapy had a favorable effect on triglyceride and LDL-cholesterol levels, i.e. it reduced them, while only minimum changes occurred in HDL-cholesterol concentrations.
In contrast, the laboratory results gathered in one of the clinical studies dealing with quetiapine have revealed elevated total cholesterol and triglycerides.

Ziprasidone

Results of a study that investigated the effect of ziprasidone on serum lipids in patients with mental retardation and behavioral disorders showed favorable ziprasidone action on lowering cholesterol and triglyceride concentrations (52).
Five short-term clinical studies that examined effects of ziprasidone in schizophrenic patients showed that ziprasidone therapy led to substantial reduction in cholesterol and triglyceride levels (53).
Presently, the number of studies and the amount of data on the effect of ziprasidone on serum lipids are insufficient to allow us to draw relevant conclusions. Actually, the highest amount of data is evidence of the fact that ziprasidone has no significant impact on cholesterol and triglyceride concentrations, or, as stated above, that it may have favorable effect on lipid concentrations in patients with previously elevated concentrations of these lipids.

Aripiprazole

Currently available information indicates that aripiprasole could have a favorable effect on serum lipid levels. Ac-

razolom promjene u koncentraciji kolesterola i triglicerida odgovaraju promjenama kod terapije placebom (54), a u nekim slučajevima primjene aripiprazola došlo je i do snižavanja koncentracija serumskih lipida, na koje je utjecalo uzimanje drugih antipsihotika (55).

Atipični antipsihotici i leptin

Povišena koncentracija leptina u serumu mijenja osjetljivost perifernih tkiva na inzulin i smatra se da bi hiperleptinemija mogla biti poveznica između pretilosti i inzulinske rezistencije (56-58).
O utjecaju atipičnih antipsihotika na leptin dostupno je vrlo malo podataka.
Utvrđeno je da klozapin i olanzapin značajnije povisuju koncentraciju leptina u serumu, kvetiapin izaziva vrlo mali, a risperidon tek minimalni porast leptina u serumu.
Iako dosad objavljene studije i ostali podatci nisu donijeli dovoljno jasne zaključke o utjecaju atipičnih antipsihotika na metaboličke parametre, možemo atipične antipsihotike rangirati prema relativnom riziku za razvoj ovih nuspojava. Ove je činjenice bitno imati na umu kod odabira antipsihotične terapije, koja je u pravilu dugotrajna.
Najveći rizik za razvoj poremećaja ravnoteže glukoze i inzulina te poremećaj vrijednosti lipida i leptina nose klozapin i olanzapin; kvetiapin je vezan uz umjeren rizik, risperidon nosi nizak rizik, dok je rizik kod ziprasidona i aripiprazola najniži.
Postavlja se pitanje kako propisivati atipične antipsihotike vodeći pri tom računa o mogućnosti pojava metaboličkih nuspojava. Navodimo preporuke za praćenje metaboličkog stanja bolesnika liječenih antipsihoticima:

1. Početno kod uvođenja antipsihotika izmjeriti antropometrijske mjere (visina, težina, obujam kukova i struka). Odrediti koncentraciju glukoze u serumu, glikolizirani hemoglobin, kolesterol, trigliceride, HDL-kolesterol, LDL-kolesterol, lipoprotein(a), apolipoprotein A1, apolipoprotein B, HDL_2-kolesterol i HDL_3-kolesterol.
2. U prva tri mjeseca liječenja antipsihotikom jednom mjesečno raditi provjeru antropometrijskih mjera te u serumu određivati glukozu, kolesterol, trigliceride, HDL-kolesterol, LDL-kolesterol.
3. U daljnjem liječenju antipsihotikom svakih šest mjeseci raditi provjeru antropometrijskih mjera te u serumu određivati glukozu, glikolizirani hemoglobin, kolesterol, trigliceride, HDL-kolesterol, LDL-kolesterol.
4. Ostale pretrage koje su početno provedene ponovo provjeravati samo ako su neki od metaboličkih parametara promijenjeni u odnosu na inicijalnu laboratorijsku obradu bolesnika.
5. Bolesnici kojima su već dijagnosticirani šećerna bolest i/ili hiperlipidemija prije početka liječenja, trebali bi biti liječeni nekim od atipičnih antipsihotika koji manje utječu na metaboličke parametre.

tually, changes in cholesterol and triglyceride levels during aripiprasole therapy were shown to be consistent with changes during placebo therapy (54); in some cases, aripiprasole administration led to a decrease in serum lipid levels which was affected by administration of other antipsychotics (55).

Atypical antipsychotics and leptin

Increased serum levels of leptin change the sensitivity of peripheral tissues to insulin, and hyperleptinemia is considered a potential link between obesity and insulin resistance (56-58).
Very little data are available on the effect of atypical antipsychotics on leptin.
It has been established that clozapine and olanzapine significantly elevate the serum level of leptin which is only slightly increased by quetiapine and minimally by risperidone.
Although past studies and other data have not offered sufficiently clear conclusions on the impact of atypical antipsychotics on metabolic parameters, atypical antipsychotics may be ranked according to the relative risk for the development of side-effects. These facts are important to keep in mind when deciding for an antipsychotic therapy which, as a rule, is a long-term one.
Clozapine and olanzapine carry the highest risk for the development of disturbance of glucose and insuline balance and of lipid and leptin levels. Quetiapine is associated with a moderate risk, risperidone with low risk, while ziprasidone and aripiprazole carry the lowest risk.
The question arises with regard to how to prescribe atypical antipsychotics while actually being aware of possible occurrence of metabolic side-effects. We state recommendations for the monitoring of metabolic status of patients treated by antipsychotics:

1. Antropometric measurements should be performed initially when introducing antipsychotic therapy (height, weight, waist and hip measurement). Glucose, glycosylated hemoglobin, cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, lipoprotein (a), apolipoprotein A1, Apolipoprotein B, HDL2-cholesterol and HDL3-cholesterol should be determined in serum.
2. Monthly check-ups of anthropometric measures should be performed during the first three months of antipsychotic therapy, together with the determination of glucose, cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol in serum.
3. During continued treatment with antipsychotics, anthropometric check-ups should be performed every six months, as well as determination of glucose, glycolysated hemoglobin, cholesterol, triglycerides, HDL-cholesterol, and LDL-cholesterol in serum.
4. Other initially performed tests should be repeated only if some metabolic parameters have been changed on comparison to initial examination.

6. Kod bolesnika kod kojih se tijekom liječenja razvije hiperinzulinemija, hiperlipidemija ili šećerna bolest tipa 2, trebalo bi isključiti dotadašnji lijek i bolesnika početi liječiti drugim antipsihotikom, čija primjena nosi manji rizik od razvoja ovih nuspojava. Ukoliko taj antipsihotik nije dovoljno učinkovit u smislu liječenja psihotičnog poremećaja, liječenje se nastavlja prethodnim lijekom, uz najmanju djelotvornu dozu. Potrebno je kontinuirano provoditi nadzor tjelesne težine i metaboličkih parametara.
7. Anamnestički treba doznati ima li bolesnik neke od simptoma šećerne bolesti, kao što su polidipsija, poliurija, gubitak tjelesne težine itd.
8. Lijekovi koji kod bolesnika izazovu veliki porast tjelesne težine trebaju biti zamijenjeni drugim lijekovima kod kojih je ovaj neželjeni učinak manje izražen.
9. Bolesnike treba poticati na promjenu životnog stila - prestanak pušenja i povećanje tjelesne aktivnosti, kako bi smanjili rizik od razvoja šećerne bolesti tipa 2.

Metaboličke nuspojave atipičnih antipsihotika sve više dolaze do izražaja i mogu imati nepovoljan utjecaj na liječenje psihičke bolesti s jedne, te tjelesno zdravlje bolesnika s druge strane. Stoga je kod propisivanja tih lijekova bitno imati na umu mogućnost javljanja metaboličkih nuspojava, prepoznati ih na vrijeme i nastaviti liječenje na racionalan način.

Adresa za dopisivanje:
Ana Kovak-Mufić
Klinika za psihijatriju
Klinička bolnica „Sestre milosrdnice"
Vinogradska 29
10 000 Zagreb, Hrvatska
e-pošta: anamufic@yahoo.com

5. Patients with diabetes and/or hyperlipidemia diagnosed prior to therapy should be treated by atypical antipsychotics that have lesser impact on metabolic parameters.
6. In patients who develop hyperinsulinemia, hyperlipidemia or type 2 diabetes during therapy, the medication administered should be discontinued and therapy should be instituted of another antipsychotic whose administration carries lower risk for the development of side-effects. If the newly introduced antipsychotic is not sufficiently effective in treating a psychotic disorder, the therapy is continued with the lowest effective dose of the previously used medication.
7. Continual monitoring of body weight and metabolic parameters is needed. Patient history should be examined for possible diabetes symptoms like polydypsia, polyuria, body weight loss, etc.
8. The drugs that induce high body weight gain in patients should be replaced by other drugs that are characterized by lesser expression of this undesirable effect.
9 Patients should be encouraged to lifestyle changes: smoking cessation and increased physical activity in order to diminish the risk for the development of type 2 diabetes.

Metabolic side-effects of atypical antipsychotics are increasingly manifested and may have negative influence on mental disease treatment on one hand, and physical welfare of a patient on the other. It is therefore important to keep in mind the possibility of occurrence of metabolic side-effects when prescribing these drugs, promptly recognize their effects, and continue with the treatment in a reasonable manner.

Corresponding author:
Ana Kovak-Mufić
Department of Psychiatry,
Sestre milosrdnice University Hospital
Vinogradska 29
10 000 Zagreb
Croatia
e-mail: anamufic@yahoo.com

Literatura/References

1. *Hiles BW. Hyperglycemia and glucosuria following chlorpromazine therapy. JAMA 1956;162:1651.*
2. *Cooperberg AA, Eidlow S. Haemolytic anaemia, jaundice and diabetes mellitus following chlorpromazine therapy. CMAJ 1956;75:746-9.*
3. *Zimmet PZ. Kelly West Lecture 1991. Challenges in diabetes epidemiology: from West to the rest. Diabetes Care 1992;15:232-52.*
4. *Olefsky JM. Insulin resistance. In: Porte D, Sherwin RS, ed. Diabetes mellitus. 5th ed. Stamford (CT): Aplleton&Lange, 1997:513-52.*
5. *Comi RJ. Drug-induced diabetes mellitus. In: LeRoith D, Taylor SI, Olefsky JM, ed. Diabetes mellitus: a fundamental and clinical text. Philadelphia (PA): Lippincott Williams&Wilkins, 2000:528-8.*
6. *Melkersson KI, Hulting AL, Brismar KE. Different influences of classical antipsychotics and clozapine on glucose-insulin homeostasis in patients with schizophrenia or related psychoses. J Clin Psych 1999;60:783-91.*
7. *Chae B-J, Kang B-J. The effect of clozapine on blood glucose metabolism. Hum Psychopharmacol Clin Exp 2001;16:265-71.*
8. *Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five year naturalistic study. Am J Psychiatry 2000;157:975-81.*
9. *Melkersson K, Dahl M. Adverse metabolic effects associated with atypical antipsychotics. Drugs 2004:64(7):701-23.*
10. *Melkerrson KI, Hulting AL, Brismar KE. Elevated levels of insulin, leptin, and blood lipids in olanzapine-treated patients with schizophrenia or related psychoses. J Clin Psychiatry 2000:61:742-9.*

11. Melkerrson KI, Dahl ML. Relationship between levels of insulin or triglycerides and serum concentrations of atypical antipsychotics clozapine and olanzapine in patients on treatment with therapeutic doses. Psychopharmacology 2003;170:157-66.
12. Lindenmayer JP, Smith RC, Singh A, Parker B, Chou E, Kotsaftis A. Hyperglycemia in patients with schizophrenia who are treated with olanzapine. J Clin Psychopharmacology 2001;21:351-3.
13. Reinstein MJ, Sirotovskaya LA, Jones LE, Mohan S, Chasanov MA. Effect od clozapine-quetiapine combination therapy on weight and glycaemic control: preliminary findings. Clin Drug Invest 1999;18:99-104.
14. Melamed Y, Mazeh D, Elizur A. Risperidone treatment for a patient suffering from schizophrenia and IDDM. Can J Psychiatry 1998;43:956.
15. Madhusoodanan S, Brenner R, Araujo L, Abaza A. Efficacy of risperidone treatment for psychoses associated with schizophrenia, schizoaffective disorder, bipolar disorder, or senile dementia in 11 geriatric patients: a case series. J Clin Psychiatry 1995;56:514-8.
16. George K, Alberti MM. Diabetic acidosis, hyperosmolar coma, and lactic acidosis. In: Becker KL, ed. Principles and practice of endocrinology and metabolism. 3rd ed. Philadelphia (PA): Lippincott Williams & Wilkins, 2001:1438-51.
17. Von Hayek D, Hüttl V, Reiss J, Schweiger HD, Füessl HS. Hyperglycaemia and ketoacidosis on olanzapine (in German). Nervenarzt 1999;70: 836-7.
18. Zajecka JM, Weisler R, Sachs G, Swann AC, Wozniak P, Sommerville KW. A comparison of efficacy, safety and tolerability of divalproex sodium and olanzapine in the treatment of bipolar disorder. J Clin Psychiatry 2002;63:1148-55.
19. Casey DE. Dyslipidemia and atypical antipsychotic drugs. The Journal of Clinical Psychiatry, 2004;65(18):237-35.
20. Meatherall R, Younes J. Fatality from olanzapine induced hyperglycaemia. J Forensic Sci 2002;47:893-6.
21. Koren W, Kreis Y, Duchowiczny K, Prince T, Sancovici S, Sidi Y, et al. Lactic acidosis and fatal myocardial failure due to clozapine. Ann Pharmacother 1997;31:168-70.
22. Koller E, Schneider B, Bennett K, Dubitsky G. Clozapine-associated diabetes. Am J Med 2001;111:716-23.
23. Koller EA, Doraiswamy PM. Olanzapine-associated diabetes mellitus. Pharmacotherapy 2002;22:841-52.
24. Koller EA, Cross JT, Doraiswamy PM, Schneider BS. Risperidone-associated diabetes mellitus: a pharmacovigilance study. Pharmacotherapy 2003; 23:735-44.
25. Ananth J, Venkatesh R, Burgoyne K, Gunatilake S. Atypical antipsychotic drug use and diabetes. Psychoter Psychosom 2002;71:244-54.
26. Taylor DM, McAskill R. Atypical antipsychotics and weight gain: a systematic review. Acta Psychiatr Scand 2000;101:416-32.
27. Russell JM, Mackel JA. Bodyweight gain associated with atypical antipsychotics: epidemiology and therapeutic implications. CNS Drugs 2001;15:537-51.
28. Sussman N. Review of atypical antipsychotics and weight gain. J. Clin Psych 2001;62(23 Suppl.):5-12.
29. Wetterling T. Bodyweight gain with atypical antipsychotics: a comparative review. Drug Saf 2001;24:59-73.
30. Nasrallah H. A review of the effect of atypical antipsychotics on weight. Psychoneuroendocrinology 2003;28:83-96.
31. Harris M, Cahill G. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039-57.
32. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
33. Meyer JM. Novel antipsychotics and severe hyperlipidemia. J Clin Psychopharmacol 2001;21:369-74.
34. Melkersson K, Hulting A-L, Brismar K. Reply: body weight gain, insulin and leptin in olanzapine-treated patients (letter). J Clin Psychiatry 2001; 62:903-4.
35. Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio PL. Diabetes mellitus in schizophrenic patients. Comphr Psychiatry 1996;37:68-73.
36. Gopalaswamy AK, Morgan R. Too many chronic mentally disabled patients are too fat. Acta Psychiatr Scand 1985;72:254-8.
37. 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;60:215-20.
38. Kelly C, McCreadie RG. Smoking habits, current symptoms, and premorbid characteristic of schizophrenic patients in Nithsdale, Scotland. Am J Psychiatry 1999;156:1751-7.
39. Lund BC, Perry PJ, Brooks JM, Arndt S. Clozapine use in patients with schizophrenia and the risk of diabetes, hyperlipidemia, and hypertension: a claim-based approach. Arch Gen Psychiatry 2001;58:1172-6.
40. Baymiller SP, Ball P, McMahon RP, Buchanan RW. Serum glucose and lipid changes during the course of clozapine treatment: the effect of concurrent beta-adrenergic antagonist treatment. Schizophrenic Res 2003;59:49-57.
41. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman B, McEvoy JP, et al. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. Am J Psychiatry 2003;160:290-6.
42. Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry 1999; 156:1270-2.
43. Spivak B, Lamschtein C, Talmon Y, Guy N, Mester R, Feinberg I, et al. The impact of clozapine treatment on serum lipids in chronic schizophrenic patients. Clin Neuropharmacol 1999;22:98-101.
44. Spivak B, Roitman S, Vered Y, Mester R, Graff E, Talmon Y, et al. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. Clin Neuropharmacol 1998;21:245-50.
45. Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J, et al. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry 2002; 59:1021-6.
46. Meyer JM. A retrospective comparison of weight, lipid and glucose changes between risperidone and olanzapine treated inpatients: metabolic outcomes after 1 year. J Clin Psychiatry 2002;63:425-3.
47. Dimelis D, Garyfallos G, Kiouniakis F et al. Olanzapine vs. risperidone: impact on weight gain and blood lipids: is there any relationship with antipsychotic efficacy? Eur Neuropsychopharmacol 2002; 12(suppl 3):S328.
48. Conley RR, Mahmoud R. A randomized double-blind study of schizophrenia or schizoaffective disorder. Am J Psychiatry 2001;158:756-74.
49. Osser DN, Najarian DM, Dufresne RL. Olanzapine increases weight and serum triglyceride levels. J Clin Psychiatry 1999;60:767-70.
50. Ishigooka J, Murasaki M, Miura S, and the Olanzapine Early-Phase II Study Group. Efficacy and safety of olanzapine, an atypical antipsychotic, in patients with schizophrenia:results of open-label multicenter study in Japan. Psychiatry Clin Neurosci 2001;55:353-63.
51. Simpson GM, Weiden P, Piggot T, et al. Ziprasidone vs olanzapine in schizophrenia: 6-month continuation study. Eur Neuropsychopharmacol 2002;12(suppl 3):S311.
52. Kurt E, Oral ET. Antipsychotics and glucose, insulin, lipids, prolactin, uric and metabolism in schizophrenia. Eur Neuropsychopharmacol 2002;12 (suppl 3):S276.
53. Cohen S, Fitzgerald B, Okos A, Khan S, Khan A. Weight, lipids, glucose and behavioral measures with ziprasidone treatment in a population with mental retardation. J Clin Psychiatry 2003;64:60-2.
54. Romano S, Cutler N, Weiden PJ, et al. Ziprasidone's effect on weight and lipids in patients with schizophrenia. Int J Neuropsychopharmacol 2002;5:S171.
55. Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Neuropsychopharmacology 1999;20:491-505.
56. Segal KR, Landt M, Klein S. Relationship between insulin sensitivity and plasma leptin concentrations in lean and obese men. Diabetes 1996;45:988-91.
57. Haffner SM, Miettinen H, Mykkanen L, Karhapaa P, Rainwater DL, Laakso M. Leptin concentrations and insulin sensivity in normoglycaemic men. Int J Obes Relat Metab Disord 1997;21:393-9.
58. Girard J. Is leptin the link between obesity and insulin resistance? Diabetes Metab 1997;23:16-24.