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Schizophrenia: Metabolic Changes and Their Management

Schizophrenia (SCH) is a psychiatric disorder characterized by disruption of both the normal thought process and the appropriate emotional response. Common clinical manifestations include hallucinations, delusions, disorganized thought, and inappropriate speech. The disorder frequently causes a marked impairment in social and occupational behavior, requiring lifelong intervention with antipsychotic medications and/or counseling. Antipsychotic drugs are effective in ameliorating symptoms and improving overall function and, therefore, are deemed to be the cornerstone of therapy in SCH subjects. However, these drugs are implicated in onset and perpetuation of obesity and a variety of metabolic abnormalities.[1-19]

This psychiatric disorder requires persistent vigilance and lifelong monitoring with individual psychological counseling and administration of antipsychotic drugs. Subjects with SCH, their families, and their caregivers require education and management skills including recurrent close monitoring with a detailed history, a thorough physical examination, and appropriate laboratory tests for onset of metabolic abnormalities as recommended by a consensus development conference conducted by several organizations.

Metabolic Disorders

Obesity is well documented to predispose to disorders of almost every organ system in the body and therefore contributes to morbidities, including disorders such as prediabetes or diabetes, hypertension, and dyslipidemia constituting metabolic syndrome, and increases mortality in the population at large. Subjects with SCH are no exception. In fact, the presence of these disorders more than doubles the relative risks of mortality in SCH patients in comparison to the general population. The mortality risk rises further with a recent documentation of increasing prevalence of cancer among subjects with both obesity and diabetes. Unfortunately, in some SCH subjects, the initial presentation of diabetes is diabetic ketoacidosis or hyperglycemic hyperosmolar state with a change in state of consciousness including coma requiring hospitalization. Thus, the severity of the clinical manifestations induced by metabolic abnormalities is often more pronounced at diagnosis in subjects with SCH as compared to non-SCH subjects and is attributed to lack of recognition of symptoms and/or neglect on the part of SCH subjects or their caregivers, leading to increased mortality. Increased prevalence of smoking in subjects with SCH contributes to recurrent infections and respiratory disorders, promoting further rise in morbidity and mortality. Finally, some of the newer antipsychotic drugs, especially olanzapine and quetiapine, are well documented to induce or exacerbate all disorders constituting metabolic syndrome, thus ensuing additional risk of morbidity and mortality.

It is well established that SCH subjects have a greater occurrence of metabolic syndrome disorders prior to treatment in comparison to the healthy population. The prevalence of these metabolic alterations rises significantly following administration of antipsychotic drugs, especially second-generation drugs. The presence of obesity, especially of visceral type as defined by several indices, was

Executive Summary

Although the treatment of schizophrenia (SCH) involving psychological therapies and antipsychotic medications is typically done under the supervision of a psychiatrist, managing medical complications of the pharmacological interventions often falls on the primary care physician.

- It is well established that SCH subjects have a greater occurrence of metabolic syndrome disorders prior to treatment in comparison to the healthy population. The prevalence of these metabolic alterations rises significantly following administration of antipsychotic drugs, especially second-generation drugs.
- Conditions such as development and aggravation of weight gain, hypertension, type 2 diabetes, osteoarthritis, sleep apnea, cardiovascular disorders, coronary heart disease, and stroke are reported. Subjects with SCH are predisposed to being overweight, and obesity and its social stigmata may further alienate SCH patients with higher risk of social withdrawal and non-compliance with pharmacological therapies.
- An expert panel concluded that atypical or second-generation antipsychotics offer significant benefits but also affirm the greatest risk of weight gain, glucose dysregulation including diabetes and its complications such as DKA, as well as dyslipidemia following treatment with clozapine, olanzapine, and quetiapine. There is an intermediate risk to administration of risperidone and the lowest risk is found with aripiprazole and ziprasidone.
- The primary care physician needs to be aware of these challenges and be an active advocate in consultation with the psychiatrist for a balanced approach to the psychiatric and medical conditions of their mutual patients.

noted to be significantly higher in SCH patients prior to drug therapy in comparison to age-matched, healthy subjects — e.g., body mass index (BMI, 26.7 kg/m^2 for SCH vs 22.8 kg/m^2 for healthy subjects, $P < 0.003$); waist:hip ratio (0.99 for SCH vs 0.86 for healthy subjects, $P < 0.005$); total body fat (34,681 mm^2 in SCH vs 27,692 mm^2 in healthy subjects, $P < 0.01$); and intra-abdominal fat (13,232 mm^2 in SCH vs 3880 mm^2 in healthy subjects, $P < 0.005$).

Obesity

The occurrence of obesity and these metabolic abnormalities appears to rise on initiation of antipsychotic therapy.[2] Unfortunately, metabolic aberrations are documented to manifest more frequently in SCH subjects even prior to treatment, and the prevalence continues to rise following treatment with antipsychotic drugs, especially the newer ones.[1-27]

The advent of obesity and the metabolic derangements constitute the metabolic syndrome and hence enhance the risk for cardiovascular and all-cause morbidities and mortality.[28-33] Thus, SCH subjects are at a much greater risk for adverse cardiovascular outcomes, including mortality.[34-40] In actuality, cardiovascular mortality is documented to be increased more than two-fold among subjects with SCH as compared to the general population. Moreover, multiple other factors also contribute to the increased mortality (*see Table 1*). The causes include lifestyle factors, such as a greater incidence of substance abuse, smoking, poor nutrition, and inactivity; coexisting illnesses, such as HIV and hepatitis C; as well as adverse effects of efficacious drugs.[41-54]

In one study, 15 SCH subjects were compared with 15 age-matched healthy volunteers. Seven SCH subjects were drug-naïve, and the remaining eight had not received oral drug therapy for at least 6 weeks and intramuscular drug administration for at least 6 months. The study documented the presence of generalized obesity as expressed by BMI and total body fat content, as well as visceral obesity as defined by waist:hip ratio and greater intra-abdominal fat in SCH patients during the drug-free period (*see Table 2*) compared to age-matched healthy volunteers.[3]

Ryan et al also demonstrated increased prevalence of visceral fat as well as prediabetes manifested by glucose intolerance or impaired fasting glucose attributed to insulin resistance as measured by a homeostasis model assessment in SCH subjects compared to normal subjects.[8,21]

A meta-analysis of more than

Table 1: Main Causes of Mortality in SCH Patients[40]

Ratio of Observed Deaths in Patients with Schizophrenia to Expected Deaths in the General Population

Cause of Death	Mortality Ratio in Men	Mortality Ratio in Women
Infectious disease	3.4	1.9
Respiratory disease	3.2	2.7
Endocrine disease	2.7	2.0
Gastrointestinal disease	2.5	2.1
Cardiovascular disease*	2.3	2.1
Urogenital disease	2.3	2.3

*Since cardiovascular disease is the most common cause of death in the general population and is more than twice as common in patients with schizophrenia, it accounts for most of the excess mortality in schizophrenia.

80 studies examined the impact of 10-week, antipsychotic drug therapy on body weight in SCH subjects.[1] The studies were divided into two groups according to drugs: 1) typical first-generation antipsychotic agents, e.g., molindone, fluphenazine, haloperidol, chlorpromazine, and thioridazine/mesoridazine; and 2) second-generation atypical antipsychotic drugs, e.g. ziprasidone, risperidone, olanzapine, and clozapine. Both groups were placebo-controlled. Weight gain was noted following treatment with all antipsychotic drugs. The only exceptions were molindone in the first-generation group and ziprasidone in the newer atypical agents; both apparently were weight-neutral. In contrast, olanzapine and clozapine appeared to induce the maximum weight gain (4.0-4.5 kg) over the course of the study. However, the weight gain was not only limited to the short-term use of the drugs.

Long-term studies confirm the lack of weight gain with ziprasidone. The weight gain with quetiapine and risperidone appeared to reach a plateau at approximately 2.0-5.6 kg (4-12 lbs), with the weight gain with olanzapine reaching peak and stabilizing at approximately 12 kg (26 lb), an increase well documented to induce significant aberrations in carbohydrate and lipid metabolism, contributing to adverse cardiovascular outcomes.[55]

Another long-term study examined weight changes with initial treatments of risperidone and olanzapine therapy over 1 year. The mean weight gain was 10.7 lbs and 17.5 lbs for patients receiving risperidone and olanzapine, respectively, at the end of 1 year, with body weights being significantly higher at the end of 1 year compared to prior initiation of either therapy.[5] Weight gain associated with antipsychotics may ensue soon after initiation of therapy; the subjects randomized to receive both olanzapine and ziprasidone gained weight within 6 weeks. However, in subjects administered ziprasidone, the weight gain was 2 lbs, significantly lower ($P < 0.001$) than the 8 lbs noted in subjects receiving olanzapine.[13]

Table 2: Adiposity in Patients with Untreated SCH[3]

Measure	Patients with Schizophrenia* (n = 15)	Healthy Controls (n = 15)	P value
Mean age (years)	33.7	30.1	NS
BMI (kg/m^2)	26.7	22.8	< 0.003
Waist:hip ratio	0.99	0.86	< 0.005
Total body fat (mm^2)	34,680.9	27,692.5	NS
Intra-abdominal fat (mm^2)	13,232.0	3879.9	< 0.005

*Patients were either drug-naive (n = 7) or had been free of oral neuroleptics for ≥ 6 weeks and IM neuroleptics for ≥ 6 months (n = 8).
NS = not significant

Weight gain following therapy with certain antipsychotics (e.g., risperidone and olanzapine) may be halted or even reversed within a short period of 6 weeks on withdrawal of these drugs and initiating therapy with ziprasidone.[6] This study involved subjects in whom therapy with either first-generation conventional antipsychotics (e.g., haloperidol) or with second-generation agents (risperidone and olanzapine) was discontinued and ziprasidone was initiated. One hundred two subjects who had prior treatment with conventional antipsychotics experienced an insignificant gain of 0.27 kg, whereas subjects who were changed from risperidone experienced a weight loss of 0.86 kg ($P < 0.0001$ vs baseline). Moreover, subjects with prior therapy with olanzapine showed a greater weight loss: 1.76 kg ($P < 0.05$ vs baseline). However, the weight loss appeared to be dependent on the body weight at the time of initiation of treatment with ziprasidone — the higher the initial body weight, the greater the weight loss.

Other Clinical Disorders

Serious clinical disorders, including hypertension, type 2 diabetes, osteoarthritis, sleep apnea, cardiovascular disorders (coronary heart disease and stroke), and cancers involving several organs, are attributed to weight gain and obesity.[34] In addition, subjects with SCH are predisposed to being overweight and obese due to lack of adequate physical activity. Moreover, the stigmatization, social rejection, and loss of self-esteem accompanying both obesity and SCH make these patients more susceptible to isolation, unfortunately leading to diminution of the interpersonal and cognitive skills required to cope with these consequences. Finally, weight gain tends to perpetuate social withdrawal and further impairs quality of life, predisposing these subjects to an additional risk for discontinuation of treatment resulting in recurrent relapses of the disorders.[34]

An increase in disorders such as hypertension, glucose intolerance including diabetes, and premature mortality secondary to weight gain similar to that induced by antipsychotic drugs is well documented in the Framingham study.[35,36] It is apparent that these disorders ensue earlier in life and with a greater prevalence, leading to enhanced risk of premature death with rising BMI > 27 kg/m^2 in subjects with SCH. The risk is further exacerbated in those receiving therapy with certain antipsychotic drugs; the death rate reaches more than 2000 excess fatalities per 100,000 individuals.[35,36] It is estimated that the lives saved due to prevented suicides may be equal to the deaths caused by disorders as a result of weight gain induced by certain drugs such as clozapine.[35,36,44]

Glucose Intolerance and Insulin Sensitivity

More frequent onset of diabetes in

comparison to the general population remains after elimination of other risk factors (e.g., obesity, family history, concomitant use of other drugs, etc.) in SCH patients.[4] Several studies have found an increased prevalence of glucose intolerance, including diabetes, in SCH patients.[14-27] A retrospective analysis documented changes in fasting glucose levels in patients administered either risperidone or olanzapine for 1 year.[5] Risperidone did not induce a significant change from baseline, but use of olanzapine was associated with an increase of 7.26 mg/dL in fasting plasma glucose concentration ($P \leq 0.05$ vs baseline). Moreover, among subjects < 60 years old, the rise in fasting glucose level with olanzapine was even greater (10.8 mg/dL) and the difference between these two age groups was statistically significant ($P = 0.03$), indicating that younger subjects may be more susceptible to prediabetes and diabetes following administration of olanzapine.[5]

To define the pathogenesis of rising plasma glucose following olanzapine treatment, an examination of glucose regulation was conducted to determine fasting plasma insulin and glucose levels in subjects with SCH or another schizoaffective disorder.[56,57] Participants were randomized to receive therapy with ziprasidone or olanzapine for 6 weeks. Plasma glucose did not change significantly with either drug, However, mean fasting plasma insulin rose by 3.3 μU/mL in olanzapine-treated subjects ($P < 0.0001$ vs baseline), whereas no significant alteration (0.25 μU/mL) from baseline was noted in patients receiving ziprasidone; the difference between insulin levels for the two drugs at the end of the observation period was significant ($P = 0.05$). Therefore, it is apparent that insulin sensitivity as determined by insulin × glucose product, a reliable index of insulin sensitivity,[58] declined following therapy with olanzapine but not with ziprasidone.[56,57]

Similar findings regarding the role of insulin resistance in glucose dysregulation following short- and long-term administration of several antipsychotic drugs are reported in several studies.[4,5,10,14-16] In an extensive retrospective study, a multivariate analysis examined the influence of other variable factors (e.g., patients' age, duration of antipsychotic treatment, use of other drugs known to affect glucose metabolism) and established that use of olanzapine, clozapine, and haloperidol induced significant glucose elevations.

Moreover, the clinical significance of the change in plasma glucose concentration is underscored by the fact that 13% of the patients treated with clozapine required a glucose-lowering agent after starting the antipsychotic, and 6% of the olanzapine group required a dose increase in their glycemic therapy. In contrast, none of the subjects in the risperidone, quetiapine, haloperidol, or fluphenazine groups required glucose-lowering intervention.[1] Mean glucose levels were higher following a long-term, continuous treatment for 2.5 years with antipsychotic drugs (e.g., olanzapine, clozapine, risperidone, quetiapine, haloperidol, or fluphenazine).[2]

Another literature review reported a markedly greater adverse impact on onset of diabetes mellitus and mortality following therapy with olanzapine (52 subjects, 3 deaths) and clozapine (30 subjects, 1 death) in comparison to subjects treated with other agents (e.g., four with quetiapine, two with risperidone, one with ziprasidone, and none with aripiprazole).[7] However, the single case reported with ziprasidone was transient hyperglycemia. This difference between various agents in occurrence of diabetes was confirmed by the FDA Medwatch surveillance system, and a greater mortality with clozapine and olanzapine was attributed to metabolic acidosis or ketosis.[7]

Cardiovascular Disease

Diabetes is deemed "cardiovascular risk equivalent" because type 2 diabetes increases the odds of SCH patients developing macrovascular disease by 2- to 4-fold compared to age-matched subjects without diabetes. The occurrence of initial myocardial infarction (MI) in subjects with diabetes is almost identical to recurrence of MI in subjects without diabetes.[28,31-33,38,39] Moreover, the fatal outcome during initial MI in subjects manifesting diabetes is not significantly different from the subjects without diabetes with a prior MI.[28] A similar pattern is also observed regarding the incidence of stroke; patients with diabetes without a prior MI manifest approximately the same risk (10.3%) as those without diabetes but with a prior MI (7.2%).[28,31,38,39] Therefore, the importance of early diagnosis and aggressive treatment to achieve prompt desirable glycemic control in delaying or preventing both micro- and macrovascular complications is never over-emphasized.

It is apparent that changes in lipids following therapy with various antipsychotic agents follows a similar path as diabetes.[2,5] The changes in total cholesterol levels were relatively small, with fluphenazine alone inducing a significant decrease of 6% from the baseline concentration. However, the alterations in triglyceride levels were more pronounced with both olanzapine and clozapine with significant rises from baseline (38% and 34%, respectively) compared to those associated with haloperidol and fluphenazine.

Fortunately, low-density lipoprotein (LDL) levels did not rise significantly when patients took the antipsychotic agents. Indeed, the patients taking olanzapine, risperidone, and quetiapine manifested significant declines of similar magnitude. Finally, the majority of the drugs apparently induced a modest, though not a significant, decline in high-density lipoprotein (HDL); the lone exception was olanzapine, which induced a significant decrease of 10%. This undesirable effect of olanzapine on HDL level may neutralize its apparent benefit regarding LDL concentration.

However, in another study, olanzapine increased fasting cholesterol by 23.6 mg/dL, a significantly greater rise than that induced by risperidone, 7.2 mg/dL. An identical

pattern was found in fasting triglycerides. Olanzapine was also associated with a markedly greater increase of 88.2 mg/dL than the 29.7 mg/dL noted with use of risperidone.[4] Fortunately, antipsychotic-induced dyslipidemia may be at least partially reversed within weeks by switching to a metabolically neutral antipsychotic agent such as ziprasidone or aripiprazole.[5-7,9,56,57,59]

In a similar nested, case-control study involving more than 1000 subjects, the use of conventional antipsychotic agents was accompanied by a small but significant increase in the risk of developing hyperlipidemia, whereas olanzapine more than quadrupled the risk with risperidone, showing no aberrant effect compared with nonuse of antipsychotics.[4] Therefore, the potential cardiovascular consequences of olanzapine therapy and its association with the metabolic syndrome warrant a serious consideration of its risk/benefit ratio prior to initiation. Another recently approved antipsychotic agent, asenapine, also presents the same dilemma regarding adverse influence on body weight, cardiovascular outcomes, and metabolic outcomes, including glycemia and serum lipid concentrations, especially because of lack of data on long-term use.[60,61]

Thus, it is apparent that subjects with SCH are more prone to manifest weight gain and its consequences, including metabolic derangements, raising the risk of adverse cardiovascular outcomes.[55] Furthermore, the risk is exaggerated with the use of various antipsychotic agents required for attaining and maintaining remission of clinical manifestations and improving quality of life in these subjects (*see Table 3*). The exact pathophysiologic mechanism responsible for occurrence of metabolic syndrome, including glycemic dysregulation with the use of these agents, may be attributed to weight gain and change in body composition and their impact on insulin sensitivity as well as beta cell dysfunction.[1,3,5,8,26,34,35]

Table 3: Metabolic Abnormalities with Atypical Antipsychotics[55]

Drug	Weight Gain	Risk of Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/–	–	–
Ziprasidone*	+/–	–	–

+ = increase, – = no effect, D = discrepant results
* Newer drugs with limited long-term data

Table 4: Recommended Frequency of Follow-up Monitoring[55]

Measurement	Baseline	4 Weeks	8 Weeks	12 Weeks	Every Quarter	Every Year	Every 5 Years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
BP	X			X		X	
FPG	X			X		X	
Fasting lipid profile	X			X			X

Consider switching to a different atypical antipsychotic if patient gains ≥ 5% of initial body weight or develops worsening glycemia or dyslipidemia

Management Strategies

Therefore, management strategies to treat and prevent or delay onset of these metabolic disorders deserve priority, especially because of their impact on all-cause mortality and specifically on cardiovascular outcomes. Several paradigms have been tested. Educational programs that involve therapeutic lifestyle changes and nutrition and exercise counseling with SCH subjects and their caregivers assist in preventing weight gain.[55,62-65] Treatment with insulin sensitizers (e.g., metformin and rosiglitazone) appears to effectively decrease BMI and body weight as well as fasting plasma insulin, which is indicative of improvement in insulin sensitivity.[66-71] Concurrent therapy with metformin and sibutramine, a weight-lowering agent, also looks promising.[72] In addition, therapy with the angiotensin receptor blockers (ARBs) valsartan and telmisartan has been shown to be beneficial with a decline in BMI, abdominal circumference, fasting insulin, and insulin resistance.[73]

Finally, a recent clinical trial using topiramate was effective in preventing weight gain and therefore delaying or decreasing the consequences of weight gain, the major one being metabolic syndrome.[74] Thus, the treatment for antipsychotic-induced metabolic syndrome is multifaceted and identical to the metabolic syndrome manifesting in the general population. Strategies should include implementing recurrent behavioral modification techniques involving

therapeutic lifestyle changes and adherence to administration of drugs including metformin, ARBs, statins, and aspirin.[75]

A Consensus Development Conference that included psychiatrists, endocrinologists, cardiologists, and experts in management of obesity was held to raise awareness and devise an algorithm for managing SCH subjects.[55] The panel concluded that atypical or second-generation antipsychotics offer significant benefits to patients with a variety of psychotic disorders. However, the panel also affirmed the greatest risk of weight gain, glucose dysregulation including diabetes and its complications such as DKA, as well as dyslipidemia following treatment with clozapine, olanzapine, and quetiapine. It noted an intermediate risk to administration of risperidone and the lowest risk with the use of aripiprazole and ziprasidone. Finally, the panel provided an algorithm of guidelines for assessing and monitoring subjects manifesting SCH prior to and following use of these effective agents to prevent and/or treat ensuing consequences of short- and long-term use of these agents (*see Table 4*).

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CME Questions

1. Hyperprolactinemia is most frequently associated with:
   a. olanzapine.
   b. qietiapine.
   c. risperidone.
   d. All of the above
2. A significant weight gain occurs most often following therapy with:
   a. aripiprazole.
   b. risperidone.
   c. haloperidol.
   d olanzapine.
3. Subjects with schizophrenia demonstrate a presence of obesity prior to treatment with antipsychotic agents as expressed by:
   a. body mass index.
   b. waist:hip ratio.
   c. total body fat content.
   d. abdominal fat content.
   e. All of the above
4. Mortality in subjects with schizophrenia manifesting diabetic ketoacidosis in comparison to subjects without schizophrenia is:
   a. increased.
   b. decreased.
   c. not different.

In Future Issues: Stroke Rehabilitation

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Evidence-based updates in primary care medicine

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Our Newest Pharmacologic Class for Treatment of Diabetes: SGLT2 Inhibitors

Source: Polidori D, et al. *Diabetes Care* 2013;36:2154-2161.

The role of the kidney in glucose regulation has been underappreciated. Although perhaps counterintuitive, after persistent exposure to elevated glucose levels in the glomerular filtrate presented to the proximal renal tubule, the kidney adapts by reabsorbing *increased* amounts of glucose, thereby *increasing* blood sugar. The sodium glucose cotransporter (SGLT2) receptor is the primary pathway for renal tubular glucose reabsorption; blockade of this receptor results in enhanced urinary glucose excretion. Currently, the only FDA-approved agent for blockade of the SGLT2 receptor is canaglifozin.

In addition to potent SGLT2 receptor blockade, it has been suspected that canaglifozin might affect intestinal absorption of glucose by its modest inhibition of intestinal SGLT1. Polidori et al tested the impact of canagliflozin SGLT1 inhibition by examining the rate of gastrointestinal glucose absorption in healthy volunteers following a 600-kcal mixed-meal tolerance test.

Canagliflozin produced a very modest reduction in glucose absorption over a 6-hour interval (about 6%). The effects were accentuated in the early postprandial intervals, indicating a slowed absorption of glucose that was not attributable to delayed gastric emptying. Blunting of early postprandial glucose absorption should have a favorable effect on postprandial glucose excursions in diabetics.

Although enhanced urinary glucose excretion is the primary mechanism of plasma glucose lowering by SGLT2 inhibitors, modest gastrointestinal SGLT1 inhibition also appears to impact postprandial glucose excursion. ■

Bariatric Surgery vs Intensive Medical Therapy for Diabetes

Source: Kashyap SR, et al. *Diabetes Care* 2013;36:2175-2182.

The benefits of bariatric surgery (BAS) are increasingly recognized for obese patients with type 2 diabetes mellitus (T2DM). Indeed, the mechanisms by which diversionary surgery (e.g., gastric bypass) produces such prompt and dramatic remission in diabetic patients are still being elucidated. Long-term observational data on BAS for persons with severe obesity (body mass index [BMI] > 40) confirm durable weight reduction, improved control of diabetes, and even suggest reduced mortality.

Few trials have directly compared the efficacy of BAS with intensive medical treatment (IMT). Kashyap et al randomized T2DM subjects (n = 60) with moderate obesity (mean BMI = 36) to one of two BAS interventions (gastric sleeve or gastric bypass) or IMT in the Surgical Therapy And Medications Potentially Eradicate Diabetes (STAMPEDE) trial. Currently reported data include outcomes at 24 months.

In essentially every category assessed, BAS patients had superior outcomes to IMT. No BAS-related deaths occurred. At 2 years, degree of A1c control, LDL, HDL, total cholesterol, triglycerides, and CRP were all more improved in the BAS patients than in the IMT patients.

When comparing outcomes in the two BAS groups, even though weight loss was similar between gastric sleeve and bypass surgery, the latter achieved greater improvements in truncal fat reduction, leptin, insulin sensitivity, beta cell function, and incretin responses. BAS is more effective for multiple metabolic markers than IMT over the long term in T2DM patients. ■

Psoriasis and Risk for New Onset Diabetes

Source: Khalid U, et al. *Diabetes Care* 2013;36:2402-2407.

Inflammatory disorders like rheumatoid arthritis (RA) and psoriasis (PSOR) have recently been confirmed to be risk factors for adverse cardiovascular (CV) events, although the precise pathways through which such risk occurs remain controversial. Some have even gone so far as to say that RA should be considered an independent CV risk factor of equal potency to the already registered risk factors like hypertension, history of premature cardiovascular death, etc. Since PSOR and RA share common inflammatory pathways, it's perhaps not surprising that both are associated with CV adversity.

To date, the relationship between PSOR and diabetes mellitus (DM) has been controversial. Since DM is a major contributor to CV events, if PSOR and

DM are related, that would account for some of the increased CV risk.

Khalid et al report on an analysis of the PSOR-DM relationship discerned through a 12-year follow-up of Danish persons ≥ 10 years (n = 4,614,807). They studied the incidence of new-onset DM in PSOR subjects vs controls. A graded linear association between PSOR and new onset DM was found. Compared to the reference population, the incidence of DM in persons with mild PSOR was almost doubled, and in severe PSOR, nearly tripled. ■

Osteoporosis: Are Two Drugs Better Than One?

Source: Tsai JN, et al. *Lancet* 2013;382: 50-56.

Most women today who are receiving pharmacotherapy for treatment of osteoporosis receive oral bisphosphonates (e.g., alendronate, risedronate). Other effective treatments, like teriparatide (TERI) and denosumab (DENO) are usually reserved for more severe cases, in some part because they require parenteral administration.

Even though osteoporosis treatments have shown risk reduction for fracture and improved bone mineral density (BMD), restoration of full bone integrity remains a challenge. As one of the few anabolic tools (as opposed to anticatabolic tools like bisphosphonates), some investigators have tried to augment the favorable activity of TERI by combination with bisphosphonates, but the results have been disappointing. Whether the addition of DENO to TERI might be beneficial was the subject of investigation by Tsai et al. Postmenopausal women with osteoporosis (n = 100) were randomized to DENO, TERI, or both for 6 months. The primary outcome of the study was improvement in BMD.

Combination TERI+DENO appeared to be synergistic, with improvements in BMD greater than either agent alone and arithmetically greater than the anticipated benefit of combined monotherapies. For example, BMD increases at the hip were 4.2% for TERI+DENO, 0.8% for TERI, and 2.1% for DENO. These data support the consideration of TERI+DENO in highest-risk patients, those unable to take other treatments, or patients who fail to respond to other regimens. ■

Long-Term Impact of Weight Management on Blood Pressure

Source: Tyson CC, et al. *J Clin Hypertens* 2013;15:458-464.

The weight loss maintenance (WLM) trial randomized adults (n = 741) with hypertension (HTN) and/or dyslipidemia — but without evidence of cardiovascular disease — to one of several weight loss management programs. Although the initial outcome reports from WLM addressed the relative efficacies of different weight loss strategies over time, this report stratified study participants into those who lost, maintained, or gained weight over the 5-year study period. Tyson et al compared blood pressure effects between the three categories of weight impact, irrespective of which particular method of weight loss had been applied.

At study end, the weight-stable group had gained 0.6 kg, as compared with a 9.1 kg increase in the weight-gain group, and a 7.1 kg decrease in the weight-loss group. The weight-stable and the weight-gain groups were noted to have similar increases in systolic blood pressure (SBP) over 5 years (SBP increase mean 4.2 mmHg), whereas the weight-loss group SBP was not statistically significantly changed.

In contrast to some other trials that report a "legacy effect" (prolonged beneficial impact of early intervention, even after the intervention has ceased), initial weight loss in WLM was not associated with favorable SBP effects if weight was regained. On the other hand, sustained modest weight reduction (< 10% of baseline BMI) had a sustained effect to maintain SBP. Although simply maintaining weight over the long term might appear to be a laudable goal, it is apparently insufficient to favorably affect SBP. ■

The WEAVE Study: Does Special Training in Domestic Violence Improve Outcomes?

Source: Hegarty K, et al. *Lancet* 2013; 382:249-258.

Intimate partner violence (IPV) is a public health problem that knows no boundaries of age, country of residence or origin, economic status, or education. Primary care clinicians, particularly family physicians, are often the first point of clinical contact for victims of IPV, but may lack confidence in their ability to identify and/or address IPV. Hegarty et al report on a trial from Australia in which women who screened positive for concerns about fear of their partner (n = 272) received care from family physicians who were randomized to receive special training in IPV or no intervention. The intervention group physicians participated in the Healthy Relationships Training program, which is intended to provide the ability to respond effectively to women who have experienced IPV and give brief counseling. The primary outcomes of the trial were changes in quality of life (as per the WHO QOL-BREF), safety planning and behavior, and mental health (as per the SF-12) at 1 year.

At 1 year, there was no difference in the primary endpoint between the intervention group and controls. A favorable impact on depression (a secondary endpoint) was seen. However, since the primary endpoint was not achieved, the potential for benefits on depression must remain considered as hypothesis generating. ■

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PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

More Side Effects of Fluoroquinolones Coming to Light

In this issue: New side effects of fluoroquinolones; probiotics and antibiotic-related diarrhea; prostate cancer risk and 5-ARIs; and FDA actions.

New study finds dysglycemia risk

Fluoroquinolones, such as levofloxacin, ciprofloxacin, and moxifloxacin, are useful broad-spectrum antibiotics, but they have been associated with tendinopathy, including tendon rupture and QT interval prolongation. Now, two new potential side effects are coming to light. In a new study from Taiwan, more than 78,000 diabetic patients who received fluoroquinolones were monitored for dysglycemia, including hyperglycemia and hypoglycemia. The study looked at users of levofloxacin, ciprofloxacin and moxifloxacin, cephalosporins, and macrolides. The absolute risk of hyperglycemia was 6.9 per 1000 for moxifloxacin and 1.6 for macrolides. The risk for hypoglycemia was 10.0 for moxifloxacin and 3.7 for macrolides. The adjusted odds ratios for hyperglycemia compared to macrolides were: moxifloxacin 2.48 (95% confidence interval [CI], 1.50-4.12), levofloxacin 1.75 (95% CI, 1.12-2.73), and ciprofloxacin 1.87 (95% CI, 1.20-2.93). For hypoglycemia, the adjusted odds ratios were moxifloxacin 2.13 (95% CI, 1.44-3.14), levofloxacin 1.79 (95% CI, 1.33-2.42), and ciprofloxacin 1.46 (95% CI, 1.07-2.00). The risk of hypoglycemia associated with moxifloxacin was even higher if patients were taking insulin. The authors suggest that fluoroquinolones, especially moxifloxacin, are associated with severe dysglycemia in diabetic patients and that clinicians should "prescribe quinolones cautiously" in diabetic patients (*Clin Infect Dis* published online August 14, 2013. DOI: 10.1093cid/cit439). In related news, the FDA is requiring labeling changes for fluoroquinolones regarding the risk of neuropathy. The FDA Drug Safety Communication states that "serious nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken and may be permanent." The warning is for both oral and parenteral forms of the drugs, but not topicals. The FDA recommends that if a patient develops symptoms of peripheral neuropathy associated with a fluoroquinolone, the drug should be stopped immediately and the patient should be switched to a non-fluoroquinolone antibiotic. Further information can be found at the FDA's website at www.fda.gov/Safety/MedWatch. ■

Probiotics and antibiotic-related diarrhea

Probiotics may not prevent antibiotic-associated diarrhea (AAD), including *Clostridium difficile* infections. That was the finding of a randomized, double-blind, placebo-controlled trial in nearly 3000 inpatients aged ≥ 65 years who were exposed to one or more oral or parenteral antibiotics. Patients were randomized to a multistrain preparation of lactobacilli and bifidobacteria or placebo for 21 days. The rate of AAD was 10.8% in the probiotic group and 10.4% in the placebo group ($P = 0.71$). *C. difficile* was uncommon and occurred in 0.8% of the probiotic group and 1.2% of the placebo group ($P = 0.35$). The authors state that "we identified no evidence that a multistrain

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

preparation of lactobacilli and bifidobacteria was effective in the prevention of AAD or CDD." (*Lancet* published online August 8, 2013. doi: 10.1016/S0140-6736(13)61218-0). An accompanying editorial wonders if this study can tip the balance of probiotic evidence, as it was a rigorously performed study vs previous small studies showing a positive effect. But, the current study used only two types of non-pathogenic bacteria (doi: 10.1016/S0140-6736(13)61571-8). Still, the cost effectiveness of routine probiotic use must be questioned based on this study. ■

Prostate cancer risk and 5-ARIs

The debate regarding 5-alpha reductase inhibitors (finasteride [Proscar] and dutasteride [Avodart]) and the risk of prostate cancer continues. Despite good evidence that the drugs reduce the overall risk of prostate cancer, there is also evidence that the drugs may increase the risk of high-grade prostate cancers (Gleason score 7-10). This was a finding of the Prostate Cancer Prevention Trial (PCPT) that was published in 2003. That finding was recently questioned in a study published in the *British Medical Journal* that found no risk of higher-grade prostate cancers (*BMJ* 2013;346:f3406, reported in the August *Pharmacology Watch*). Now, 10 years after the PCPT was originally published as an 8-year study, the 18-year follow-up has been published in the *New England Journal of Medicine*. Of the nearly 19,000 men who underwent randomization in the PCPT, prostate cancer was diagnosed in 10.5% of the finasteride group and 14.9% of the placebo group, a 30% reduction in the rate of prostate cancer (relative risk 0.70; 95% CI, 0.65-0.76; $P < 0.001$). But all of the reduction was in lower-grade prostate cancers. There was a slightly higher rate of high-grade cancer in the finasteride group (3.5% vs 3.0%, $P = 0.05$), but there was no difference in overall mortality. There was also no increase in mortality in men diagnosed with high-grade prostate cancer. The authors conclude that finasteride reduced the risk of prostate cancer by about one-third, and although high-grade cancer was more common in the finasteride group, there was no difference in overall mortality or survival after the diagnosis of prostate cancer (*N Engl J Med* 2013;369:603-610). Dutasteride was also studied in the REDUCE trial and similarly found lower rates of low-grade prostate cancers but increased rates of higher-grade cancers (*N Engl J Med* 2010;362:1192-1202). Some have argued that the higher rate of high-grade cancers is due to higher surveillance and "detection bias," but regardless of the cause, it is reassuring to know that there is no higher risk of mortality, at least in the PCPT. The FDA changed the labeling to both finasteride and dutasteride in 2011 regarding the increased risk of high-grade prostate cancers. ■

FDA actions

The FDA has issued a Drug Safety Communication regarding a case of progressive multifocal leukoencephalopathy (PML) in a patient who was taking fingolimod (Gilenya) for the treatment of multiple sclerosis. This is the first reported case of PML associated with fingolimod in patients who had not previously taken natalizumab (Tysabri). The patient, who lives in Europe, had been on the drug for about 8 months and had previously taken interferon beta-1a, azathioprine, and steroids. Novartis, the manufacturer of fingolimod, indicated it is possible that the patient had PML prior to starting the drug. PML is a rare neurologic disease caused by latent infection with the JC virus. It has been associated with immunosuppressive drugs, including natalizumab.

The FDA has approved a new topical agent to treat facial redness in adults with rosacea. Brimonidine, an alpha-2 agonist, is currently used as an ophthalmic preparation for treating glaucoma. The drug constricts dilated facial blood vessels for up to 12 hours. It is approved in a 0.33% topical gel that is applied once daily. Patients with depression, coronary artery disease, Raynaud's, or other conditions that may be exacerbated by an alpha agonist should use the drug with caution. Brimonidine gel is marketed by Galderma as Mirvaso.

The FDA has approved dolutegravir, a new once-daily HIV integrase inhibitor. It is the third integrase inhibitor on the market after raltegravir and elvitegravir. The drug is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infections in adults and children ≥ 12 years of age weighing at least 40 kg. It may be used in treatment-naïve patients or treatment-experienced patients, including those who have previously taken an integrase inhibitor. Approval was based on four trials in more than 2500 patients that showed efficacy in combination with other antiretrovirals. A fifth trial showed efficacy in HIV-infected children as young as 12 who had not taken an integrase inhibitor. Dolutegravir is marketed by ViiV Healthcare as Tivicay. ■