

TREATING THE WHOLE PATIENT: SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND METABOLIC SYNDROME

There has been mounting concern about metabolic syndrome in modern psychiatry and mind-body medicine. The metabolic syndrome, also known as syndrome X (obesity, impaired glucose metabolism, dyslipidemia, hypertension, hypercoagulability) has been linked to the development of cardiovascular disease and type 2 diabetes which are associated with an increase in health care costs as well as with excessive morbidity and all-cause mortality (Kinder et al. 2004). In United States an estimated 23.7% of adults, without difference between men and women, meet criteria for the metabolic syndrome, making this an intense focus of research among epidemiologists and clinicians (Ford et al. 2002). Not only poor diet and decreased physical exercise have been linked to its development, but various medications (antipsychotics, antidepressants, protease inhibitors, etc.). Psychiatric patients seem to have a higher predisposition and prevalence of this syndrome than general population and there is a link between the metabolic syndrome and premature death in psychiatric patients. Many reports have speculated that depression may be linked to adverse health outcomes through an association with metabolic syndrome (Kinder et al. 2004). Therefore, it is pertinent for psychiatrists in everyday practice to identify those patients at risk or those presenting with the metabolic syndrome. On the other side, depression is common in medical patients and often goes untreated or undertreated. Failure to recognize and treat depression in patients with the metabolic syndrome may have deleterious physiological as well as psychological consequences. Addressing the syndrome and its various symptoms will help clinicians to treat the patient as a whole and improve overall morbidity and mortality.

Depression and metabolic syndrome

Several lines of evidence have indicated the common association of depression with decreased hippocampal volume, cardiovascular disorders, hypertension, osteoporosis and diabetes (Brown et al. 2004). The prevalence of cardiovascular disorders and diabetes is higher in depressed subjects than that in the general population (Robertson & Katona 1997). On the other side, the prevalence of depression is several times higher in diabetic subjects as well as in subjects with coronary heart disease (CHD) than that in general population. Depression also may accelerate the onset of serious and fatal complications of these diseases.

Recent studies have demonstrated that depression constitutes a major and independent risk factor in the development of cardiovascular disorders and type 2 of diabetes mellitus. It seems that depression may lead to the development of cardiovascular disease and diabetes through its association with the metabolic syndrome. This syndrome is a risk factor for the development of cardiovascular disease and type 2 of diabetes mellitus (Brown et al. 2004).

A number of plausible mechanisms have been hypothesized to underlie the relationship between depression and metabolic syndrome: lifestyle (behavioral) risk factors (smoking, alcoholism, physical hypoactivity, obesity-increased food consumption), physiological risk factors (HPA dysregulation, ANS dysregulation, platelet hyperactivity). However, there are few studies examining the relationship between depression and the metabolic syndrome (Kinder et al. 2004).

SSRIs and metabolic syndrome

SSRIs are proposed first-choice medications for treatment of major depression. These

medications are currently considered the safest to use with cardiac patients, in contrast with tricyclics, which may alter heart rate and rhythm (Lett et al. 2004). Some clinical studies indicate that SSRIs are better antidepressants for diabetic patients than other medications (Musselman et al. 2003).

SSRIs and platelet reactivity. The modulation of platelet activity has been suggested as a potential mechanism responsible for the possible reduction of cardiovascular mortality in depressed patients treated with SSRIs (Serebruany et al. 2003, Lederborg et al. 2003). Platelet activity is an important factor in the development of atherosclerosis, acute coronary syndrome, and thrombosis, and anti-platelet medications have been used as secondary prevention for CHD (Lett et al. 2004). In addition to reducing symptoms of depression, SSRIs have anticoagulation attributes, which may be effective in reducing risk for cardiac events in susceptible patients with CHD (Lett et al. 2004). Normalization of platelet activation was described in depressed patients treated with paroxetine (Musselman et al. 2000).

The SSRIs interfere with serotonin accumulation in platelets, and SSRI treatment normalizes elevated indices of platelet activation and aggregation in patients with depression and CHD. The antiplatelet effect of the SSRIs is neither associated with the antidepressant effect of the medication, nor does resolution of depression immediately normalize increased platelet activity if the treatment is not an SSRI medication. In a study comparing paroxetine with nortriptyline in depressed patients with CHD, baseline indices of platelet activity, specifically platelet factor 4 and beta-thyroglobulin, were elevated in patients with depression and CHD compared with patients with CHD alone and normal control subjects (Pollock et al. 2000). Treatment with paroxetine normalized the increased indices of platelet activity, and this effect occurred with low doses of paroxetine and before any discernable antidepressant effect of the medication. In contrast, although nortriptyline was a very effective antidepressant in this group of patients,

there was no reduction in the heightened platelet activity in nortriptyline-treated patients.

Cardiovascular effects of the SSRIs. SSRIs are the preferred treatment for depression and anxiety comorbid with cardiovascular disease, based on clinical data and cardiovascular profile (Ballenger et al. 2001). With respect to cardiac effects in depressed patients without heart disease, SSRIs in general do not change significantly cardiac conductance and blood pressure (Roose 2003). Heart rate may be elevated by some SSRIs (Roose 2003) with mild anticholinergic (paroxetine) and noradrenergic (fluoxetine, paroxetine) activity or decreased by fluvoxamine (Tucker et al. 2000) which has no noradrenergic and anticholinergic effects. Blood pressure may be slightly increased by fluoxetine and paroxetine (Roose 2003) as well as slightly decreased by fluvoxamine (Tucker et al. 2000).

A number of epidemiologic studies give indirect evidence that SSRIs may reduce the risk of ischemic attacks (Roose 2003). A number of epidemiologic studies give indirect evidence that this antiplatelet effect of SSRIs may reduce the risk of ischemic events. In a study comparing the rate of MI in patients treated with a SSRI or no antidepressant, the SSRI-treated patients had a significantly lower rate of MI than did the non-SSRI treated patients (Sauer et al. 2001). This lower MI rate may not simply be due to a reduction of psychiatric symptoms, inasmuch as a comparison of patients treated with medication had no reduction in the rate of MI. The SSRIs may represent an attractive alternative or addition to other anti-platelet drugs that are being combined with aspirin, such as ticlopyridine and dipyridamol. The mortality benefits of SSRIs have been linked with their antidepressant properties, regulation of sympathetic and parasympathetic balance, and modulation of vascular tone via dopamine and noradrenaline blockade (Serebruany et al. 2003).

SSRIs and glucose metabolism. Treatment with antidepressant drugs can directly interfere with glucose level or may interact with hypoglycemic agents. The tricyclic antidepressant

sants may lead to hyperglycemia, to an increase carbohydrate craving (from 86% to 200%), and impaired memory. SSRIs may be hypoglycemic (causing as much as a 30% decrease in fasting plasma glucose) and anorectic (causing an approximately 2-lb decrease), while possibly improving alertness. There have been six studies of fluoxetine, at dose of 60mg/day pursued up to 12 months that have demonstrated that medication's usefulness in diabetic patients, with reductions in weight (to 9.3kg), in FPG (to 45mg%), and in HbA1c (to 2.5%). In studies in comorbid diabetes mellitus and depression, nortryptiline, a norepinephrine reuptake inhibitor that produces increased synaptic catechols, has lead to worsenig of indices of glucose control (Goodnick 2001).

Fluoxetine improves insulin sensitivity beyond the effect mediated through weight loss and the effects of fluoxetine on insulin sensitivity may be achieved by increased glucose uptake and glycogen synthesis in the soleus muscle tissue (Park & Choi 2002).

SSRIs and weight. Clinicians should always have in mind potential beneficial or detrimental effects on appetite and weight when choosing among available antidepressants. Several possible pharmacological mechanisms have been postulated to account for weight gain with antidepressants, including carbohydrate craving related to increased alpha noradrenergic activity, antagonism of histamine H1 i serotonin 5-HT2C receptors, activation of the TNF-alpha sytem and leptin (Hinze-Selch et al. 2000). For many years it has been known that increasing the availability of serotonin in synaptic cleft reduces food consumption, while decreasing serotonin receptor activation brings about the opposite effect. Before the SSRIs era, almost all the antidepressants in use were liable to cause the weight gain. The SSRIs as a group have an appetite-suppressing effect, at least acutely in the short term, and may cause nausea and vomiting. The nausea usually subsides within a few days but a mild suppression of appetite, as opposed to the increased that may be brought about by tricyclics, mirtazapine,

trazodone, etc., may remain. Fluoxetine is the most anorexigenic of the SSRIs because it shows direct 5-HT2C agonist activity. It is important to have in mind that over time weight gain on some SSRIs (e.g. paroxetine) may occur as a delayed-onset effect and sometimes may be dramatic.

Conclusion

The SSRIs as a class of medications, might be expected to have a favorable effect regarding metabolic syndrome and decrease mortality because of their significant antiplatelet effects, favorable cardiovascular and glyceimic activities. Although the SSRIs evidently share the same mechanism of action, therapeutic and overall side-effects profiles, individual patients may react very differently to one SSRI versus another with regards weight gain, cardiovascular and glyceimic effects. Clinicians have been cautioned to consider potential beneficial or deprimental effects on metabolic syndrome when choosing among available antidepressants.

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