Clinical Briefs in Primary Care™

The essential monthly primary care update

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Establishing the CV Safety Profile of ADHD Meds in Children and Young Adults

Source: Cooper WO, et al. *N Engl J Med* 2011;365:1896-1904.

Case reports of adverse cardiovascular (CV) events in children and young adults taking attention deficit-hyperactivity disorder (ADHD) medications have included myocardial infarction (MI), stroke, and sudden death. These individual cases, however, neither prove causation nor provide insight into event frequency, since the denominator is unknown. Because of the seriousness of these events, a clearer understanding of their epidemiology is important.

Cooper et al performed a retrospective cohort study based on data from four large health plans, which included data from more than 1 million persons 2-24 years of age. Among this population, there were data on 373,667 person-years of ADHD drug treatment in these children and young adults.

In this entire population, there were 81 serious CV events (rate = 3.1/100,000 person-years). However, persons currently using ADHD drugs did *not* demonstrate an increased risk for CV events compared to non-users; in fact, the hazard ratio (HR) demonstrated a trend (not statistically significant) toward *fewer* serious CV events in persons taking ADHD medications (HR = 0.75). Whether CV events were looked at in composite (MI + stroke + sudden death) or individually, the same generally favorable trend was seen (HR = 0.70, *P* = NS). Similarly, former users of ADHD medications were at no greater risk for CV events than never-users. This study was not funded by industry, but by the federal agencies AHRQ and FDA. ■

If You're Already on a Statin, Does Adding Niacin Help?

Source: AIM-HIGH Investigators. *N Engl J Med* 2011;365:2255-2267.

Results from intervention trials with statins for secondary prevention of cardiovascular (CV) events are consistently impressive. Nonetheless, significant residual risk remains; that is, even though statin treatment reduces risk of events by as much as 20-30% over 5 years, persons with existing CV disease are still at substantially greater risk of having another CV event than age-matched controls without CV disease. Observational studies suggest that increasing high-density lipoprotein (HDL) might provide an even greater incremental CV risk reduction than LDL modulation, although evidence from interventional trials is conflicting.

The AIM-HIGH trial enrolled patients with existing CV disease (n = 3414) who were already receiving simvastatin (plus ezetimibe if LDL goals were not attained with simvastatin alone). Study subjects were randomized to extended-release niacin or placebo.

Although intended to conclude after 4.6 years, the study was stopped early (at 3 years) subsequent to the recommendation by the data and safety monitoring board that the trial be discontinued due to both a lack of positive efficacy as well as an unanticipated elevation of ischemic stroke in niacin recipients. Adding niacin to statins in persons with stable atherosclerotic vascular disease does not reduce CV events. ■

Adverse Effects on Semen from SSRI Treatment of Premature Ejaculation

Source: Koyuncu H, et al. *Int J Impot Res* 2011;23:257-261.

Several treatments have been shown to be highly effective in management of premature ejaculation (pEJ), including behavioral therapy, systemic modulation of serotonin, and topical agents. The most popular current treatment is sustained use of selective serotonin reuptake inhibitors (SSRIs), which typically increase intravaginal latency (the time from intromission to ejaculation) from pretreatment times of < 1 minute to over 5 minutes. There has been little study of the impact of SSRI treatment on parameters such as semen, perhaps because most of the pEJ trials have been short-term. Studies in which SSRIs are added to semen preparations in vitro have shown adverse changes in sperm motility and viability, prompting consideration of potential adverse effects from systemically administered SSRIs.

Escitalopram is an SSRI sometimes used to treat pEJ. To elucidate the effects of escitalopram on semen, subjects with lifelong pEJ (n = 25) and normal baseline semen analysis were enrolled. Additionally, at baseline all subjects had normal scrotal ultrasound, CBC, glucose, hormone levels, lipid levels, and genito-rectal examinations.

At 1 month, no alterations in semen were detected. However, at 3 months there were multiple statistically significant changes: sperm count decreased (68 million/mL to 26 million/mL), number of motile spermatozoa decreased by more than 50%, and the number of morphologically normal sperm decreased by over 50%. In the absence of a control group, these findings cannot be considered definitive. Additionally, it is possible that sperm function might return to pretreatment levels upon drug discontinuation. However, the prominent effects on semen within a short interval merit our awareness. ■

Comparing Two High-Intensity Statin Regimens: Atorvastatin and Rosuvastatin

Source: Nicholls SJ, et al. *N Engl J Med* 2011;365:2078-2087.

Between statin head-to-head trials are uncommon. The PROVE-IT trial convincingly demonstrated that intensive LDL reduction with atorvastatin (achieved LDL = 62 mg/dL) vs pravastatin (achieved LDL = 95 mg/dL) improved outcomes in persons with acute coronary syndromes. In persons with stable atherosclerotic disease, however, it remains controversial whether high-dose statin treatment reduces mortality when compared with "standard" dosages, even though it has been shown to reduce CV events.

Results from clinical trials are sometimes hampered by the limitations of time: In a 5-year window of opportunity, are the long-term effects of intervention adequately represented? Such time limitations have prompted consideration of surrogate markers, which might more promptly reflect the anticipated long-term effects of intervention. Accordingly, Nicholls et al performed a controlled trial (n = 1039) to compare, by means of intravascular ultrasound, the effects of high-dose atorvastatin (80 mg/d) vs rosuvastatin (40 mg/d) on coronary atherosclerosis.

At 2 years, atheroma regression was similar between the two agents, despite the superior performance of rosuvastatin for attained LDL (62.6 mg/dL vs 70.2 mg/dL) and HDL (50.4 mg/dL vs 48.6 mg/dL). Maximal doses of these statins appear to perform similarly for the endpoint of regression of atherosclerosis. ■

The Effect of Adiposity on Insulin Pharmacodynamics

Source: Porcellati F, et al. *Diabetes Care* 2011;34:2521-2523.

It is probably not a surprise to clinicians that adiposity and efficacy of therapeutic insulins are related. We are accustomed to seeing type 2 diabetes (DM2) associated with being overweight and obesity, and watching control of diabetes become more difficult if obesity worsens. The question addressed by Porcellati et al is not whether insulin requirements are affected by obesity, but rather are various insulins differently affected by obesity.

To that end, DM2 subjects (n = 18) were studied using infusions of glucose to maintain constant plasma levels. Three different insulins — NPH, insulin glargine, and detemir — were compared. The threshold at which glucose infusion rates were meaningfully different was a body mass index (BMI) > 29 kg/m^2, at which point all three insulins demonstrated less efficacy to control glucose. That is, as BMI goes up, insulin sensitivity goes down.

Within this study group, however, there was a statistically significantly greater reduction in insulin sensitivity with detemir than with either NPH or insulin glargine. Ultimately, this means that in patients with progressively greater BMI, a higher dose of detemir may be required to achieve glucose control than the other two forms of basal insulin. Some clinical trials have also reflected this requirement for greater doses of detemir than comparators in patients with obesity. Nonetheless, because the amount of data addressing this issue remains small, whether there are meaningful differences that need to be considered when addressing insulin needs of obese DM2 patients in reference to choice of basal insulin is still considered a matter of controversy. ■

Psoriasis Predisposes to Serious Infections

Source: Wakkee M, et al. *J Am Acad Dermatol* 2011;65:1135-1144.

As the use of systemic immune-modulating treatments for rheumatoid arthritis (RA) has evolved, the risk for serious infectious disease complications related to their use has become more evident. Since many of the drugs used to treat RA are now used for patients with psoriasis (PSR), it is logical to evaluate PSR patients for risk of serious infectious diseases.

Wakkee et al looked at a database comprised of PSR patients (n = 25,742) and controls (n = 128,710) from a Dutch registry compiled from 1997-2008. They examined the incidence of infectious disease events resulting in hospitalization during this interval.

Overall, persons with PSR were more than twice as likely to be hospitalized for a serious infectious disease than controls; multivariate analysis (adjustment for confounding issues like age, diabetes, COPD) modified this hazard ratio slightly (down from 2.08 to 1.54).

Perhaps the greatest surprise from this trial was that the use of systemic antipsoriatic medications was *not* associated with risk for infectious disease. Apparently then, it is PSR itself which imposes an increased risk of infectious diseases, not the immunosuppressive agents increasingly used to treat it. ■

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