Childhood Sleep Deficits Linked to Weight Gain

BY KATE JOHNSON Montreal Bureau

hildren who lose sleep may have an increased risk of gaining weight, according to findings of a new study.

This points to the importance of sleep in the fight against obesity and further fuels the argument for later starts to the school day, reported Emily K. Snell and colleagues in Child Development.

"Encouraging parents to put their younger children to bed earlier at night and allowing both younger and older children to sleep longer in the morning, as well as urging school districts to avoid very early school start times for later elementary and middle school aged children, might represent an important and relatively low cost strategy to reduce child-hood weight problems," wrote Ms. Snell of the Department of Human Development and Social Policy and the Institute

for Policy Research at Northwestern University, Chicago (Child Development 2007;78:309-23).

In a study of 2,281 children from a nationally representative survey called the Child Development Supplement of the Panel Survey of Income Dynamics, the children were aged 3-12 years at baseline and 8-17 years at follow-up. Time diaries were used on a randomly selected weekday and weekend to record sleep behavior, and then a subsample of 1,441 children were examined to see whether sleep behavior at baseline influenced weight at follow-up.

The study found "a large decline in weekday sleep across middle childhood and adolescence, driven largely by later weekday bedtimes," a finding that the researchers described as "troubling." While they recommend a minimum of 10-11 hours of sleep per night for younger children, a goal which the study subjects usually achieved on weekends, children as young as 7 years old were already falling short on weeknight

VYTORIN® (ezetimibe/simvastatin) Brief Summary of Prescribing Information CONTRAINDICATIONS Hypersensitivity to any component of this medication. Active liver disease or unexplained persistent elevations in serum transaminases (see WARNINGS, Liver Enzymes).

or unexplained persistent elevations in serum transaminases (see VVARVINGs, Liver Enzymes). Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolernia. Moreover, cholesterol and other products of the cholesterol bosynthesis pathway are essential components for tetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as simvastain to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, VYTORIN is contraindicated during pregnancy and in nursing mothers. VYTORIN should be administered to women of childbearing age only when such patients are highly unlikely to conceive. If the patient becomes pregnant while taking this drug. VYTORIN should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*). WARNINGS WARNINGS

this drug, V/TORIN should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*). WARNINGS Myopathy/Rhabdomyolysis: In clinical trials, there was no excess of myopathy or rhabdomyolysis associated with ezetimible compared with the relevant control arm (placebo or HMG-CoA reductase inhibitor alone). However, myopathy and thabdomyolysis are known adverse reactions to HMG-CoA reductase inhibitors and other lipic-lowering drugs. In clinical trials, the incidence of CK >10 × the upper limit of normal [ULN] was 0.2% for VYTORIN. (See PRECAUTIONS, *Skeletal Muscle*.) Simvastatin, like other inhibitors of HMG-CoA reductase, notically causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above 10 × ULN. Myopathy sometimes takes the form of habdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of HMC-CoA reductase inhibitory activity in plasma. As with other HMG-CoA reductase inhibitors, the risk of myopathy/fhabdomyolysis dose related. In a clinical trial database in which 41,050 at least 4 years, the incidence of myopathy was approximately 0.00%, 0.08% and 0.53% at 20, 40 and 80 mg/day, respectively. In these trials, patients were carefully monitored and some interacting medicinal products were excluded. All patients starting therapy with VYTORIN or whose dose of VYTORIN is being increased, should be advised of the risk of myopathy and told to report promptly any unexplained muscle pain, there exis of myopathy and told to report promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with simvastatin threaps esolved when simvastatin threatment was promptly discontinued. Periodic CK determinations may be considered in patients starting therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-stand

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telithromycn is unavoidable, unclopy when a construction the course of treatment. Other drugs: Gemfibrozil, particularly with higher doses of VYTORIN, and other fibrates: The safety and effectiveness of ezetimibe administered with fibrates have not been established. Therefore, the concomitant use of VYTORIN and fibrates

Other drugs: Gemitbrozit, particularly with higher doses of VY1ORIN, and other fibrates: The safety and effectiveness of sectimibe administered with fibrates have not been established. Therefore, the concomitant use of VYTORIN and fibrates should be avoided. There is an increased risk of myopathy when simvastatin is used concomitantly with fibrates (sepecially gemitbrozit). The combined use of simvastatin with gemitbrozit brains of the concomitant were of VYTORIN and fibrates should be avoided. Unless the benefits are likely to outweigh the increased risk of this drug combination. The dose of simvastatin should not exceed 100 mg daily in patients receiving concomitant medication with gemitbrozit. Therefore, although not recommended, if VYTORIN is used in combination with gemitbrozit, the dose should not exceed 100 mg daily. (See PRECAUTIONS, *Drug Interactions, Other drug interactions, Fibrates.*)
Niacin (=1 g/day): Caution should be used when prescribing lipid-lowering doses (=1 g/day) on lanci with VYTORIN, as nacin can cause myopathy when given alone. The benefit of further alterations in lipid levels by the combined use of VYTORIN should not exceed 10/10 mg daily in patients receiving concomitant medication with with nicain cause myopathy when given alone. Cyclosporine or danazol with higher doses of VYTORIN: The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving concomitant medications with predoson or danazol should be carefullyweighed against the oftent sick of these combinations. Gee PRECAUTIONS, *Drug Interactions*. JUTORIN: The dose of VYTORIN should not exceed 10/20 mg daily in patients receiving concomitant medications with minodarone or verapamil with higher doses of VYTORIN: The dose of VYTORIN should not exceed 10/20 mg daily in patients receiving concomitant medications. Amiodarone or verapamil should be carefullyweighed against the oftent dails of the site of VYTORIN. The dose of VYTORIN is should and esceed 10/20 mg daily in patients receiving concomitant medications with m

Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Fibrates*	Avoid VYTORIN		
Cyclosporine Danazol	Do not exceed 10/10 mg VYTORIN daily		
Amiodarone Verapamil	Do not exceed 10/20 mg VYTORIN daily		
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)		
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VYTORIN* (ezetimibe/simvastatin) Liver Enzymes In 3 placebo-controlled, 12-week trials, the incidence of consecutive elevation

Liver Enzymes In 3 placebo-controlled, 12-week trials, the incidence of consecutive elevations (\pm 3 × ULN) in serum transaminases was 1.7% overall for patients treated with WTORIN and appeared to be dose-related with an incidence of 2.6% for patients treated with VTORIN 10/80. In controlled long-term (48-week) extensions, which included both newly-treated and previously-treated patients, the incidence of consecutive elevations (\pm 3 × ULN) in serum transaminases was 1.8% overall and 3.6% for patients treated with VTORIN 10/80. These elevations in transaminases were generally asymptomatic, not associated with cholestasis, and returned to baseline after discontinuation of therapy or with continued treatment. It is recommended that liver function tests be performed before the initiation of treatment with VTORIN, and thereafter when clinically indicated. Patients that due to 10/80-mg dose should receive an additional test prior to titration, 3 months after titration to the 10/80-mg dose, and periodically threatter (egs. semiannually) for the first year of treatment. Platents who develop increased transminase levels should be monitored with a second liver function tests until the abnormativ(cs): Pturn to normal. Should an increase in AST or ALT of 3 × ULN or greater persist, withdrawal of therapy with VYTORIN is recommended. VYTORIN should be used with cautoin in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or uneplained before with a final function. The disease is out to be 0.7000 with the disease or uneplained the forty early of the final transminase levels on the use of VYTORIN. **PRECAUTIONS**

alcohol and/or have a past history of liver disease. Active liver diseases or unexplained persistent transaminase elevations are contraindications to the use of VHORIN. **PRECAUTIONS** *Information for Patients*: Patients should be advised about substances they should not take concomitantly with VHORIN and be advised to report promptity unexplained muscle pain, tenderness, or weakness (see below and WARNINGS, *Myopathy/Rhabdomyolysis*). Patients should also be advised to inform other physicians prescribing a new medication that they are taking VHORIN. *Skeletal Muscle*: In post-marketing experience with exetimibe, cases of myopathy and rhabdomyolysis have been reported regradless of causality. Most patients who developed rhabdomyolysis such as fibrates. *Hepatic Instificancy*: Due to the unknown effects of the increased exposure to exet in be addition of exetimable to agents known to be associated with increased risk of rhabdomyolysis, such as fibrates. *Hepatic Instificancy*: Due to the unknown effects of the increased exposure to exet initible in patients with moderate or severe hepatic insufficiency. VYTORIN *Interactions*.

ezetimibe in patients with moderate or severe hepatic insufficiency, VYTORIN is not recommended in these patients. Drug Interactions VYTORIN: CP3A4 Interactions: Potent inhibitors of CYP3A4 (below) increase the risk of myopathy by reducing the elimination of the simvastatin component of VYTORIN. See WARNINCS, Myopathy/Rhabdomyolysis. Itraconazole, ketoconazole, large quantities of grapefruit juice (>1 quart daily). Interactions with lipid-lowering drugs that can cause myopathy when given alone See WARNINGS, Myopathy/Rhabdomyolysis. The risk of myopathy is increased by gemfbrozil and to a lesser extent by other fibrates and naion (nicotinic acid) (>1 g/da). Datacol: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of danazol particularly with higher doses of VYTORIN (see WARNINGS, Myopathy/Rhabdomyolysis). Amodorone or Verapamit: The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone or verapamil with higher doses of VYTORIN (see WARNINGS, Myopathy/Rhabdomyolysis). Cholestyramine: Concomitant holestyramine administration decreased the mean AUC of total ezetimibe approximately 55%. The incremental LDL-C reduction due to adding. VYTORIN to cholestyramine may be reduced by this interaadon. Cyclosporine: The risk of myopathy/thabdomyolysis is increased by concomitant administration of cyclosporine particularly with higher doses of VYTORIN (see WARNINGS, Myopathy/Rhabdomyolysis). Cholestyramine: Concomitant by the particularly with higher doses of VYTORIN (see WARNINGS, Myopathy/Rhabdomyolysis). Cholestyramine: Concomitant by the particularly with higher doses of VYTORIN (see WARNINGS, Myopathy/Rhabdomyolysis). Cholestyramine: concomitant to holestyramine administration. Cyclosporine: The risk of myopathy/thabdomyolysis is increased the mean AUC of total ezetimibe approximately 55%. Caution should be exercised when using VYTORIN and cyclosporine concomitant administratin of cyclosporine particularly

MypadhyRhabdomyöyss). Caution should be exercised when using VYTORIN and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Cyclosporine concentrations should be monitored in patients receiving VYTORIN and cyclosporine. The degree of increase in zeztimibe exposure may be greater in patients with severe renal insufficiency. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by zeetimibe. In a pharmacokinetic study in post-renal transplant patients with mildy impaired or normal renal function (creatinin earance of >50 mL/mn). concomitant cyclosporine administration increased the mean

exposite to externine trom concornitant uses should be carefully Weigned against inte benefits of alterations in lipid levels provided by exetimible. In a pharmacokinetic study in post-renal transplant patients with mildly impaired or normal renal function (creatinine decarance of 250 ml/rmi). comomilant cydosporine administration increased the mean AUC and C__ of total exelimible 3.4-fold (range 2.3- to 7.9-fold) and 3.9-fold (range 3.0-to 4.4-fold), respectively. In a separate study, the total exelimible and 3.9-fold (range 3.0-to 4.4-fold), respectively. In a separate study, the total exelimite procure increased 12-fold in one renal transplant patient with severe renal insufficiency receiving multiple medications, including cydosporine. (See WARNINCS, *MiopathyRhaddomyolysis*). *Digovin:* Concomitant administration of a single deso 6 digovin in healthy male voluntees receiving simvastain resulted in a sight elevation (-C0.3 ng/mL) in plasma digovin concentrations compared to concomitant administration of plaseba and digovin. Patents taking digovin should be monitored appropriately when V/TORIN si initiated. *Fibrates:* The safety and effectiveness of V/TORIN administered with fibrates have not the galibladet bile. Coadministration of V/TORIN with fibrates is not recommended until use in patients is studied. (See WARNINCS, *MiopathyRhaddomyolysis*). *Wartain::* Simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the protinombin time, reported a International Normalized Raio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in a normal volunteer study and in a hypercholesterolemic patient study, respectively. Which other statins, clinically evident bleeding and/or increased prothornbin time has been reported fin a few therapy to ensure that no significant alteration of prothrombin time should be determined before starting VYTORIN and frequently enough during early therapy to ensure that no significant alteration of prothrombin time in patients not taking antico

(INR) in patients who had ezetimibe added to warfarin. Most of these patients were also on other medications. The effect of VYTORIN on the prothrombin time has not been studied. *Exetimibe: Fenolibrate:* In a pharmacoknetic study, concomitant tenofibrate administration increased total exetimibe concentrations approximately 15-fold. *Gemfibrozii:* In a pharmacoknetic study, concomitant gemfibrozii administration increased total exetimibe concentrations approximately 15-fold. *Simusstatin: Programolo:* In healthy male volunteers there was a significant decrease in mean C_{max} but no change in AUC, for simusatatin total and achie inhibitors with concomitant administration of single doses of simusatatin and propranolol. The clinical relevance of this finding is unclear. The pharmacokinetics of the enantiomers of propranolo were not affected. *CNS Toxicity* Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin

CNS Toxicity Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day. A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug

VUTORIN* (ezetimibe/simvastatin)
 also produced vesibulocochiear Walleran-like degeneration and retinal ganglion cell dromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.
 CNS vascular lesions, characterized by peivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels fibrin deposits and necrosis of small vessels were seen indogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels fibrin deposits and necrosis of small vessels were seen drugs of this class.

 There were cataracts in female rats after 2 years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after 3 months at 90 mg/kg/day (19 times) and at 2 years at 50 mg/kg/day (5 times).

 Caronogenesis, Mutagenesis, Impairment Of Fertility VYTOR/IN: No animal caronogenicity or fretility studies have been conducted with the combination of ezetimibe and sinvastatin. The combination of ezetimibe with sinvastatin did not show evidence of dastogenicity was observed in vitro in a thromosomal aberation assay in human peripheral blood lymphocytes with ezetimibe and sinvastatin with or without metabolic adviation. There was no evidence of genotoxicity at doses up to 500 mg/kg/day (C150 times the human exposure at 10 mg daily based on AUC _{0.2447} for total ezetimibe). A 104-week dietary carcinogenicity with or and sinvastatin in the *in vitro* in a diversion and speriation assay in human peripheral blood MUC _{0.2447} for total ezetimibe). A 104-week dietary carcinogenicity study with ezetimibe was conducted in mice at doses up to 500 mg/kg/day (C150 times the human exposure at 10 mg daily based on AUC _{0.2447} for total ezetimibe). No evidence of mutagenicity

In a 2-year study in rais at 2- mg/kg/gay, inter was a statistically significant increase in the incidence of thryoid follicular adenomas in female rate sposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC). Asecond 2-year rat carinogenicity study with doese of 50 and 100 mg/kg/day produced heptaccellular adenomas and carinomas (in female rats at both doeses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doese; thyroid follicular cell acrinomas were increased in males at 100 mg/kg/day. Thyroid follicular cell carinomas were increased in males at 100 mg/kg/day. Thyroid follicular cell carinomas were increased in males at 100 mg/kg/day. Theroid follicular cell carinomas were increased in males at 100 mg/kg/day. The increased incidence of thyroid incoplams appears to be consistent with findings from other HMG-CoA reductase inhibitors. These treatment levels represented plasm adrug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (temales) the mean human plasma drug exposure after an 80-mg daily dose. No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse live metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in viro* alkaline elution assay using rat hepatocytes, a/2-79 ammalian cell forward mutation study, aniv *invi* or homosome aberation study in CHO cells, or an *in viro* chromosomal aberation assay in mouse bone marrow. There was decreased fertility in male rats treated with simwastatin for 34 weeks at 25 mg/kg/bdy weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day), however, this effect was not observed during a subsequent fertility study in winch simwastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenice synthesitered at this significance of spermatogenic epith

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Directions, we believery Labor and Delivery The effects of VYTORIN on labor and delivery in pregnant women are unknown. *Nursing Mothers* In rat studies, exposure to ezetimibe in nursing pups was up to half of that observed

VYTORIN® (ezetimibe/simvastatin) in maternal plasma. It is not known whether ezetimibe or simvastatin are excreted into human breast milk. Because a small amount of another drug in the same class as simvastain is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women who are nursing should not take VYTORIN (see CONTRAINDICATIONS). Pediatric Use WTORIN: There are insufficient data for the safe and effective use of VYTORIN in pediatric patients (See Ezetimibe and Simvastatin below). Exertimibe: The pharmacokinetics of ezetimibe in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with retelmbe in the pediatric Opulation is limited to 4 patients (9 to 17 years) with homozygous stosterolemia and 5 patients (11 to 17 years) with hoFH. Treatment wepreince with retelmbe in a controlled dinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse experience profile generally similar to that of patients treated with simvastatin and on adverse experience profile generally similar to that of patients treated with placebo. Doses >40 mg have not been studied in this population. In this limited controlled study, there was no detectable effect on growth or sexual maturation in the adolescent boys or girls, or any effect on menstrual cycle length in girls. Adolescent theys should be courseled on appropriate contraceptive methods while on therapy with simvastatin (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls. *Ceriatic Use* Of the patients who received VYTORIN in clinical studies, 792 were 65 and older (this

Studied in patients younger than 10 years of age, nor in pre-menarchal girts. Geriatric Use Of the patients who received VYTORIN in clinical studies, 792 were 65 and older (this included 176 who were 75 and older). The safety of VYTORIN was similar between these patients and younger patients. Greater sensitivity of some older individuals cannot be ruled out. (See ADVERSE REACTIONS.) ADVERSE REACTIONS WYTORIN has been evaluated for safety in more than 3800 patients in clinical trials. WYTORIN was generally well tolerated. The table below summarizes the frequency of clinical adverse experiences reported in $\approx 2%$ of patients treated with VYTORIN (n=1256) and at an incidence greater than placeboo Clinical Adverse Events Occurring in $\approx 2%$ of Patients Treated with VYTORIN and at an incidence Greater than Placebo, Regardless of Causality* Body Systemy Placebo (%) Exetimibe Simvastatir (%) VYTORIN (%) Organ Class

Organ Class	10 mg (%)					
Adverse Event	n=311	n=302	n=1234	n=1236		
Body as a whole – general disorders						
Headache	6.4	6.0	5.9	6.8		
Infection and infestations						
Influenza	1.0	1.0	1.9	2.6		
Upper respiratory	2.6	5.0	5.0	3.9		
tract infection						
Musculoskeletal and connective tissue disorders						
Myalgia	2.9	2.3	2.6	3.5		
Pain in extremity	1.3	3.0	2.0	2.3		
* Includes 2 placebo-controlled combination studies in which the active ingredients equivalent to						

VYTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered All doses

VYTORIN were coadministered and 1 placebo-controlled study in which VYTORIN was administered. † Al does: Post-marketing Experience: The adverse reactions reported for VYTORIN are consistent with those previously reported with exetimibe and/or simvastatin. Exetimite: Other adverse experiences: reported with exetimibe in placebo-controlled studies, regardless of causality assessment: Body as a whole – general disorders: faigue; Costrointestinal system disorders: abdominal pain, diarther, Infection and infestations: infection viral, pharyngitis, sinusitis, Musculoskeletal system disorders: athralgia, back pain; Respiratory system disorders: coughing. Post-marketing Experience: The following adverse reactions have been reported in post-marketing experience, regardless of causality assessment: Hypersensitivity reactions, including anaphylaxis, angoedemar, rash, and urticaria; arthralgia; elevations in liver transaminases; hepatitis; thrombocytopenia; pancreatitis; nausea; cholelithiasi; cholecystitis; elevated creatine phospholinase; and, very rarely, myopathy/rhabdomyolysis (see WARNINCS, Myopathy/Rhabdomyolysis). Simvastatin: Other adverse experiences reported with simvastatin in placebo-controlled dinical studies, regardless of causality assessment. Body as a whole – general disorders: asthenia; Eye disorders: catarat; Castrointestinal system disorders: abdominal pain, constipation, diarrhea, dyspepsia, flatuleen, nausea; Skin and subcutaneous bisue disorders: eczema, pruritus, rash. The following effects have been reported with other HMG-CoAreductase inhibitors. Not all the effects listed below have necessarily been associated with asthemate in meastatin therapy.

The following effects have been reported with other HIMC-CAA reductase inhibitors. Not all the effects listed below have necessarily been associated with simwastait in therapy Musculoskeletal system disorders: muscle cramps, myalgia, myopathy, rhabdomyolysis, and an another state of the sta ligias. *us system disorders:* dysfunction of certain cranial nerves (including alteration of taste

arthralgas. Nervous system disorders: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances. *Ear and labyrinth disorders:* vertigo. *Psychiatric disorders:* analyby, insomnia, depression, loss of libido. *Phycerschistiv Reactions:* An apparent hypersensitivity synchrome has been reported rarely which has included 1 or more of the following features: anaphylaxis, anguedema, lupus erythematous-like synchrome polymalgian heumatica, dermatomycostis, vasculitiks, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESK increase, essnophilia, arthritis, arthralgia, utricaria, asthenia, photosensitivity, fever, chila, flushing, malaise, dyspnea, taxic epidermal necrolysis, eythema multiforme, including Stevens-Johnson synchrome. *Castrointestinal system disorders:* apnreatitis, vomiting. *Hepatobilitry disorders:* hepatitis, including for honic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fullminant hepatic necrosis, and hepatoma. *Skin and subcutaneous tissue disorders:* apoexia. *Skin and subcutaneous tissue disorders:* agnecia. *Skin and subcutaneous* tissue disorders: gynecomasia, erectile dysfunction. *Eye disorders:* progression of cataratis (lens opacilies), ophthalmoplegia. *Laboratory Honormalities:* elevated transminases, alkaline phosphatase, y-glutamyl transpeptidase, and bilirubin; thyroid function abnormalities. *Laboratory Fest* Marked persistent increases of serum transaminases have been neoted. (Reventings)

Laboratory Tests Marked persistent increases of serum transaminases have been noted (see WARNINGS, Liver Enzymes). About 5% of patients taking simvastatin had elevations of CK levels of 3 or more times the normal value on 1 or more occasions. This was attributable to the noncardiac fraction of CK Muscle pain or dysfunction usually was not reported (see WARNINGS, Myopathy/Rhaddomyo/pisi). Concomitant ind/Laweina Therany

ARNINGS, Myopathy/khabdomyoyss). ncomitant Lipid-Lowering Therapy controlled clinical studies in which simvastatin was administered concomitantly with olestyramine, no adverse reactions peculiar to this concomitant treatment were observed. adverse reactions that occurred were limited to those reported previously with simvastatin

or cholestynamine. Adolescent Patients (ages 10-17 years) In a 48-week controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age with heterozygous familial hypercholesterolernia (n=175), the safey and tolerability profile of the group treated with simustatin (10-40 mg daily) was generally similar to that of the group treated with placebo, with the most common adverse experiences observed in both groups being upper respiratory infection, headache, abdominal pain, and nausea (see PRECAUTIONS, *Pediatric Use*).

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sleep. "The fact that a substantial portion of American children achieve such small amounts of sleep should be of concern in light of findings from prior studies suggesting associations between poor sleep hygiene and decreased cognitive and social functioning," they wrote.

The investigators also noted that "the shift towards later weekday bedtimes might begin earlier than some researchers have suspected," occurring in preadolescence, as early as age 8 or 9 years. "There is clear evidence for the appropriateness of later bedtimes for adolescents, as these changes ... may be biologically driven. ... For younger children, however, the change

to later bedtimes may be driven more by social factors rather than changes in biology," they suggested.

The study also found that lost sleep shows up on the scales 5 years later with later bedtimes for younger children (aged 3-7.9 years) having the most impact on subsequent body mass index (BMI),

while later wake times were more important for older children (aged 8-12.9 years) and subsequent BMI. "Even 1 additional hour of sleep may have a significant and meaningful effect on BMI and overweight

status," they wrote, noting that at baseline, 1 extra hour of sleep above average lowered a child's risk of being overweight 5 years later—from 36% to 30%, even after controlling for baseline BMI, family socioeconomics, and

race. The study found no evidence that gender or physical activity influenced the effect of sleep on BMI.

The mediating pathway between inadequate sleep and weight gain may be the disruption of hormones that regulate appetite and metabolism, suggested the authors, "with insufficient sleep hours causing reduced levels of leptin and increased levels of ghrelin, a hormonal profile associated with increased hunger and appetite for carbohydrate-rich foods."

The investigators suggested that a combination of strategies geared toward earlier bedtimes and later wake times depending on a child's age "might well improve multiple aspects of children's health, emotional well-being, and academic performance."

Neonatal Weight Gain Linked to Adult Obesity

CHICAGO — Rapid weight gain in the first week of life in formula-fed infants is associated with increased risk of obesity 2-3 decades later, Dr. Nicolas Stettler said at the annual scientific sessions of the American Heart Association.

"The neonatal period may be a sensitive period for the programming of energy balance regulation," said Dr. Stettler of Children's Hospital of Philadelphia.

He presented an observational study conducted over several decades. It involved 653 formula-fed white infants born in the Iowa City area. At age 20-32 years, 32% of them were overweight or obese.

Using a relatively recent statistical analysis method called life-course modeling, Dr. Stettler and coworkers were able to identify the first 8 days of infancy as a critical period of weight gain associated with adult obesity.

The median weight gain during the first 8 days of life was about 200 g. After the researchers adjusted for birth weight, maternal overweight, and other potential confounders, early weight gain remained an independent predictor of adult overweight; for each 100-g increase in weight, the risk of adult overweight or obesity rose by about 28%. This was true even among babies with a low birth weight and rapid catch-up.

Thus, an individual who gained 200 g in the first week of life had a 32% chance of becoming an overweight adult, one who gained 300 g had a 41% risk, and a 400-g weight gain was associated with a 55% risk, Dr. Stettler said.

The importance of this large study of early weight gain isn't so much that it permits identification of individuals at risk for adult obesity; after all, obesity is now so common. Rather, the study is important mainly for its public health and research implications. The results, Dr. Stettler said, may eventually open the door to novel brief interventions in infancy to prevent later obesity. For example, the findings are consistent with animal studies that suggest overfeeding in the first few days of life may result in neurologic or endocrinologic imprinting leading to later obesity.

The first week of life is the first time an individual has to regulate energy intake, he noted. During the fetal period, nutrients are provided passively.

Know the risk

Younger adolescents are also at increased risk for meningococcal disease¹

Recommend vaccination to reduce the risk

The mediating pathway

sleep and weight gain

may be the disruption of

hormones that regulate

appetite and metabolism.

between inadequate

- Menactra vaccine is highly immunogenic following a single 0.5mL intramuscular injection^{1,2}
- Produces a strong booster response in adolescents previously vaccinated against meningococcal disease²



(Groups A,C,Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

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Protect them as if they were your own— Talk with patients today about meningococcal disease and the benefits of vaccination

Safety Information

Menactra vaccine is indicated for active immunization against invasive meningococcal disease caused by *N meningitidis* serogroups A, C, Y, and W-135 in persons 11 through 55 years of age. Menactra vaccine will not stimulate protection against infection caused by *N meningitidis* other than serogroups A, C, Y, and W-135. As with any vaccine, vaccination with Menactra vaccine may not protect 100% of individuals.

There are risks associated with all vaccines. The most common adverse reactions to Menactra vaccine include pain, redness, and induration at the site of injection, headache, fatigue, and malaise. Menactra vaccine is contraindicated in persons with known hypersensitivity to any component of the vaccine or to latex, which is used in the vial stopper. Guillain-Barré Syndrome (GBS) has been reported in temporal relationship following administration of Menactra vaccine. Persons previously diagnosed with GBS should not receive Menactra vaccine. Because any intramuscular injection can cause injection site hematoma, Menactra vaccine should not be given to persons with any bleeding disorder, such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefits clearly outweigh the risk of administration. If the decision is made to administer Menactra vaccine to such persons, it should be given with caution, with steps taken to avoid the risk of hematoma formation following injection. Before administering Menactra vaccine, please see brief summary of full Prescribing Information on adjacent page.

References: 1. Sanofi Pasteur Inc. Data on file (Study MTA02). September 2003. MKT9271-1. 2. Keyserling H, Papa T, Koranyi K, et al. Safety, immunogenicity, and immune memory of a novel meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV-4) in healthy adolescents. Arch Pediatr Adolesc Med. 2005;159:907-913. *CPT is a registered trademark of the American Medical Association.

Menactra vaccine is manufactured and distributed by Sanofi Pasteur Inc

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