

Poor Sleep May Predict Major Depression Risk

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SAVANNAH, GA. — Poor sleep quality might be a modifiable risk for depression; moreover, many biomarkers associated with depression also are associated with poor sleep.

Poor sleep quality before interferon-alpha

treatment appeared to predict which subjects would develop depressive symptoms, Dr. Francis E. Lotrich of the University of Pittsburgh reported during a symposium on geriatric depression.

The findings, which might have broader implications for geriatric depression, come from ongoing National Institute of Mental Health-funded research into interferon-induced depression.

Interferon-alpha therapy can induce

major depression in about 25% of people within a few months of starting treatment, he said. Researchers prospectively followed a cohort of nondepressed hepatitis C patients about to receive interferon-alpha. Subjects were drawn from several overlapping studies and cohorts, Dr. Lotrich said in an interview; so far, researchers have followed over 100 patients.

Pretreatment with selective serotonin reuptake inhibitors (SSRIs) might help

prevent depression in some, but is not universally effective. Initial data suggest that those having elevated symptoms of depression might be the subset of people who benefit from using an SSRI to prevent interferon-induced depression.

Preliminary findings suggest that genetic polymorphisms in the serotonin transporter—and possibly in interaction with other genetic polymorphisms in other serotonin genes—can help predict the risk of major depressive disorder (MDD) in younger adults.

In older adults (for this presentation, aged 50 years and older), genetic polymorphisms in growth factor genes (such

Table 3. Incidence and Rate of Hypoglycemia^a in Placebo-Controlled Clinical Studies when JANUVIA was used as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin), Regardless of Investigator Assessment of Causality

Add-On to Glimepiride (+/- Metformin) (24 weeks)	JANUVIA 100 mg + Glimepiride (+/- Metformin)	Placebo + Glimepiride (+/- Metformin)
	N=222	N=219
Overall (%)	27 (12.2)	4 (1.8)
Rate (episodes/patient-year) ^b	0.59	0.24
Severe (%) ^c	0 (0.0)	0 (0.0)
Add-On to Insulin (+/- Metformin) (24 weeks)	JANUVIA 100 mg + Insulin (+/- Metformin)	Placebo + Insulin (+/- Metformin)
	N=322	N=319
Overall (%)	50 (15.5)	25 (7.8)
Rate (episodes/patient-year) ^b	1.06	0.51
Severe (%) ^c	2 (0.6)	1 (0.3)

^aAdverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.

^bBased on total number of events (i.e., a single patient may have had multiple events).

^cSevere events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to pioglitazone study, the overall incidence of adverse reactions of hypoglycemia was 1.2% in patients treated with JANUVIA 100 mg and 0.9% in patients treated with placebo.

In the study of JANUVIA as add-on combination therapy with metformin and rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on JANUVIA and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on JANUVIA and 1.0% in patients given add-on placebo.

In the 24-week, placebo-controlled factorial study of initial therapy with JANUVIA in combination with metformin, the incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients given JANUVIA alone, 0.8% in patients given metformin alone, and 1.6% in patients given JANUVIA in combination with metformin.

In the study of JANUVIA as initial therapy with pioglitazone, one patient taking JANUVIA experienced a severe episode of hypoglycemia. There were no severe hypoglycemia episodes reported in other studies except in the study involving co-administration with insulin.

Laboratory Tests. Across clinical studies, the incidence of laboratory adverse reactions was similar in patients treated with JANUVIA 100 mg compared to patients treated with placebo. A small increase in white blood cell count (WBC) was observed due to an increase in neutrophils. This increase in WBC (of approximately 200 cells/microL vs placebo, in four pooled placebo-controlled clinical studies, with a mean baseline WBC count of approximately 6600 cells/microL) is not considered to be clinically relevant. In a 12-week study of 91 patients with chronic renal insufficiency, 37 patients with moderate renal insufficiency were randomized to JANUVIA 50 mg daily, while 14 patients with the same magnitude of renal impairment were randomized to placebo. Mean (SE) increases in serum creatinine were observed in patients treated with JANUVIA [0.12 mg/dL (0.04)] and in patients treated with placebo [0.07 mg/dL (0.07)]. The clinical significance of this added increase in serum creatinine relative to placebo is not known.

Postmarketing Experience. The following additional adverse reactions have been identified during postapproval use of JANUVIA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions include anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome [see *Warnings and Precautions*]; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis [see *Limitations of Use, Warnings and Precautions*].

USE IN SPECIFIC POPULATIONS

Pregnancy. *Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to JANUVIA while pregnant. Health care providers are encouraged to report any prenatal exposure to JANUVIA by calling the Pregnancy Registry at (800) 986-8999.

Sitagliptin administered to pregnant female rats and rabbits from gestation day 6 to 20 (organogenesis) was not teratogenic at oral doses up to 250 mg/kg (rats) and 125 mg/kg (rabbits), or approximately 30- and 20-times human exposure at the maximum recommended human dose (MRHD) of 100 mg/day based on AUC comparisons. Higher doses increased the incidence of rib malformations in offspring at 1000 mg/kg, or approximately 100 times human exposure at the MRHD.

Sitagliptin administered to female rats from gestation day 6 to lactation day 21 decreased body weight in male and female offspring at 1000 mg/kg. No functional or behavioral toxicity was observed in offspring of rats.

Placental transfer of sitagliptin administered to pregnant rats was approximately 45% at 2 hours and 80% at 24 hours postdose. Placental transfer of sitagliptin administered to pregnant rabbits was approximately 66% at 2 hours and 30% at 24 hours.

Nursing Mothers. Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when JANUVIA is administered to a nursing woman.

Pediatric Use. Safety and effectiveness of JANUVIA in pediatric patients under 18 years of age have not been established.

Geriatric Use. Of the total number of subjects (N=3884) in preapproval clinical safety and efficacy studies of JANUVIA, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly, and it may be useful to assess renal function in these patients prior to initiating dosing and periodically thereafter. [See *Dosage and Administration*.]

For detailed information, please read the Prescribing Information.

Rx only



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'We can treat sleep. Can we treat depression by treating sleep?'

DR. LOTRICH

as BDNF) might help predict who is more at risk for major depressive disorder, he said. In addition, among older adults, elevations in other inflammatory cytokines, such as interleukin-6, might help predict who is at greater risk for MDD.

What emerged across all age groups is that poor sleep quality can predict who is at risk for MDD. Poor sleep quality before interferon-alpha treatment appeared to predict depression. Moreover, many of the genes and blood-based biomarkers that predict depression are associated with poor sleep as well. "Poor sleep explained everything," Dr. Lotrich said.

He cautions, however, that whether addressing poor sleep quality can prevent interferon-induced depression—or, for that matter, other types of depression—remains to be determined. "We can treat sleep," Dr. Lotrich said. "Can we treat depression by treating sleep?" ■

Disclosures: Dr. Lotrich's research has been funded by the NIMH.



Genes and biomarkers that predict depression also are tied to poor sleep.