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Treating Depression and Reducing Thoughts of Suicide in Older Adults

Contributing faculty for this article: **George S. Alexopoulos, MD**

Nearly one in ten older adults in the United States experiences some form of depression, and a fifth of them contemplate suicide. Two-thirds of older patients are treated by primary care physicians, but many of those with depression remain untreated or fail to adhere to prescribed treatment.

Results from the Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT) have demonstrated for the first time that integrating a trained depression care manager into the primary care of older patients increased the number of patients receiving treatment, led to a higher remission rate of depression, and reduced suicidal thoughts compared with patients who received usual care over a two-year period. The findings were published in the August volume of the *American Journal of Psychiatry*.

"Depression multiplies the risk of death in people with major diseases such as cancer, heart disease, and stroke. In older individuals, depression is not just an inconvenience—it is a lethal illness," explained lead author George S. Alexopoulos, MD, Director of the Weill Cornell Institute of Geriatric Psychiatry at NewYork-Presbyterian Hospital/Westchester Division and Professor of Psychiatry at Weill Cornell Medical College, who collaborated with researchers from the University of Pittsburgh and the University of Pennsylvania. "Treating depression is an important part of preventing medical illness." In fact, a 2007 report from the PROSPECT study showed that patients with major depression who received treatment had a 45 percent lower mortality rate than patients who received usual care.

The PROSPECT study compared outcomes between 320 patients aged 60 years and older who received care from a trained depression care manager (a social worker, nurse, or psychologist trained in PROSPECT procedures) in their primary care physicians' offices and 279 patients who received usual care from their primary care physicians. Care was provided in 20 primary care practices in the states of New York and Pennsylvania.

Depression care managers helped physicians offer treatment according to accepted practice guidelines, monitored treatment response, and provided follow-up over two years. Treatment included antidepressants and/or psychotherapy, and care managers encouraged patients to adhere to therapy.

see Treating Depression, page 8

Scientists Create Mouse Model of Parkinson's Disease

Contributing faculty for this article: **M. Flint Beal, MD, Chenjian Li, PhD, and Robert E. Burke, MD**

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital have created the first mouse model of Parkinson's disease (PD), which not only is based on the most common genetic defect in PD patients, but also successfully reproduces the impaired mobility and degenerative brain changes that occur in human disease. The model will facilitate studies of PD pathogenesis and also serve as a useful tool for assessing new therapies. The research was published in the July 2009 issue of *Nature Neuroscience*.

"To really study disease effectively, we need animal models that recapitulate the disease phenotype," explained Chenjian Li, PhD, Assistant Professor of Neuroscience at Weill Cornell Medical College, the paper's senior author and the model's creator. "In the

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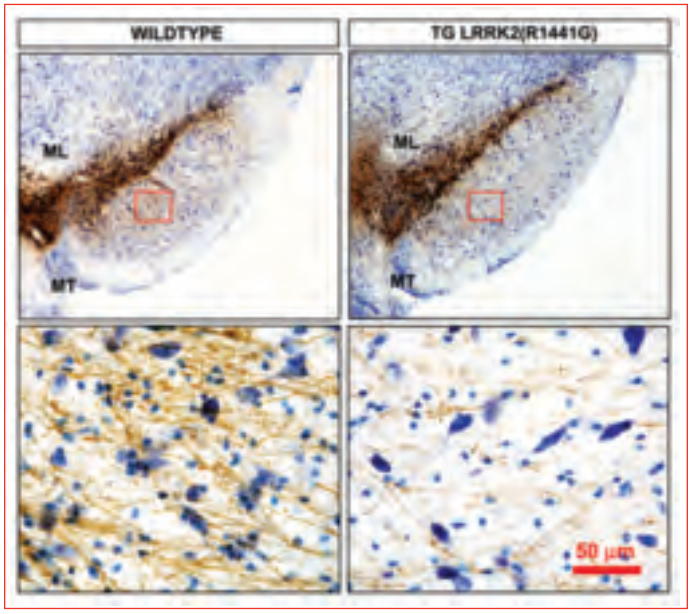

Morphologic abnormalities of mesencephalic dopamine neurons and their axons in LRRK2R1441G BAC transgenic mice. Tyrosine hydroxylase immunostaining of ventral mesencephalon. ML, medial lemniscus; MT, medial terminal nucleus. Rectangles in the upper panels are shown at a higher magnification in the lower panels. LRRK2R1441G BAC transgenic mice showed a loss of tyrosine hydroxylase-positive dendrites in substantia nigra pars reticulata and a reduction of tyrosine hydroxylase neuron size in SNpc.

"We now have a mouse model based on the known genetic cause of Parkinson's disease in which we can see neurodegenerative features."

—Robert E. Burke, MD

field of Parkinson's disease, however, accurate animal models have been missing—until now."

"This model will help us decipher the pathways underlying the development of Parkinson's disease, identify new therapeutic targets, and evaluate novel treatment approaches," added study co-author M. Flint Beal, MD, the Anne Parrish Titzell Professor of Neurology and Professor of Neurology and Neuroscience at Weill Cornell Medical College.

Mouse models for Parkinson's disease based on genetic causes have existed for years, but in no case did a model appropriately mirror the clinical changes observed in PD patients. Dr. Li and his colleagues used an approach called bacterial artificial chromosome (BAC) technology to introduce large fragments of a mutant form of the human *LRRK2* (leucine-rich repeat kinase-2) gene into mouse zygotes.

Mutations in *LRRK2* are the most common genetic defects identified in PD patients; some 38 percent of Ashkenazi Jews, for example, have a sporadic *LRRK2* mutation. An autosomal dominant inherited form has also been associated with familial PD.

Mice bred to have the *LRRK2* mutation were compared with those that had wild-type *LRRK2*. At three months of age, the two groups of mice had no differences in body weight, brain weight, or motor activity. But by 10 to 12 months of age, mice with mutant *LRRK2* displayed age-dependent and progressive motor activity deficits, with reduced mobility similar to that seen in PD patients who have hypokinesia. Other symptoms typically seen in patients—such as tremors, rigidity, and postural instability—were not observed in the *LRRK2* mutant mice.

"This model will help us decipher the pathways underlying the development of Parkinson's disease, identify new therapeutic targets, and evaluate novel treatment approaches."

—M. Flint Beal, MD

Moreover, the motor deficits were reversed with the administration of levodopa and apomorphine, a dopamine agonist—confirming that the *LRRK2* mutant mice recapitulated the progressive motor deficits and responsiveness to levodopa that are characteristic of human PD.

The investigators also found that the mice with impaired mobility experienced impaired dopamine release resulting from axonal disintegration. "The cardinal features of Parkinson's disease are impaired motor function and degenerative effects in the dopaminergic system," said study co-author Robert E. Burke, MD, the Alfred and Minnie Bressler Professor of Neurology and Pathology at Columbia University College of Physicians and Surgeons, and Pathology Director of Research Laboratories for Parkinson's Disease at NewYork-Presbyterian/Columbia University Medical Center, whose laboratory analyzed the brain tissue of the mice. "We didn't see either of these features in previous mouse models, making them unacceptable. We now have a mouse model based on the known genetic cause of Parkinson's disease in which we can see neurodegenerative features."

The research team is now using the mouse model to study the mechanisms underlying PD development. They are exploring the timing, location, and causes of the axonopathy observed in the mutant mice to learn more about the observed neurodegenerative changes. They've also received many inquiries from pharmaceutical companies eager to pursue drug evaluation studies utilizing the new mouse model.

For example, Dr. Beal noted that laboratories and pharmaceutical companies are developing kinase inhibitors for PD treatment. He also said he intends to evaluate coenzyme Q10 (an antioxidant nutriceutical) and creatine—two drugs currently under study in clinical trials of PD patients—to see what types of response might occur in the mutant mice. Future studies could potentially identify drugs to use in people with the *LRRK2* mutation who don't yet have PD symptoms to see if they can delay disease onset, slow its progression, or ideally prevent it from developing at all.

Concluded Dr. Burke, "This model is what this field has needed for decades."

Video footage displaying the impaired mobility of the LRRK2 *mutant mice is available on the* Nature Neuroscience *Web site: www.nature.com/natureneuroscience.*

Can a Vaccine Prevent Brain Cancer Recurrence?

Contributing faculty for this article: **Theodore H. Schwartz, MD, and Rose Lai, MD, MSc**

Glioma, the most common and most deadly type of malignant brain tumor, is devastating for patients and their families. Patients usually live to about a year or more with current standard therapy including surgery to reduce the tumor, radiotherapy, and temozolomide both during and six months post radiotherapy. Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital and many other institutions are working toward more effective treatments for glioma, including those that harness the immune system.

Building on the promising results of earlier trials of a vaccine called CDX-110, Theodore Schwartz, MD, a neurosurgeon at NewYork-Presbyterian/Weill Cornell Medical Center, and Rose Lai, MD, MSc, a neuro-oncologist at NewYork-Presbyterian/Columbia University Medical Center, are both enrolling patients in a Phase II multicenter trial (ACT III) of the vaccine. CDX-110 targets the growth factor receptor EGFRvIII, which is expressed on the tumor cells of about 25 percent of patients with glioma.

"In the earlier trials, a number of patients did very well for 1½ years to two years," said Dr. Lai. "The latest data from those trials show promising median survival, as well as overall survival. Median time to disease progression was 16.6 months and estimated median overall survival was 33.1 months. In the historical control group, median time to progression was 6.3 months and median overall survival was 15 months. In these earlier Phase II trials the survival benefit is considerable."

The ACT III study will look at the effectiveness of CDX-110 plus temozolomide in patients newly diagnosed with glioma. "Patients will first have surgery to remove the tumor, and then they go into the standard of care therapy, six weeks of radiation and oral temozolomide," said Dr. Schwartz. "Two weeks after that is complete, they get their first of three injections of the vaccine, each two weeks apart. Patients will continue to get one injection per month for the rest of their lives along with temozolomide once a month as maintenance therapy."

"Because there is evidence that the vaccine can potentiate the effect of the temozolomide, the monthly vaccine is scheduled for a week before the temozolomide," said Dr. Lai.

The study, initially designed as a randomized 2:1 trial of treatment or temozolomide, has been reconfigured so that all patients who enroll get the vaccine. Study subjects will be compared to historical controls.

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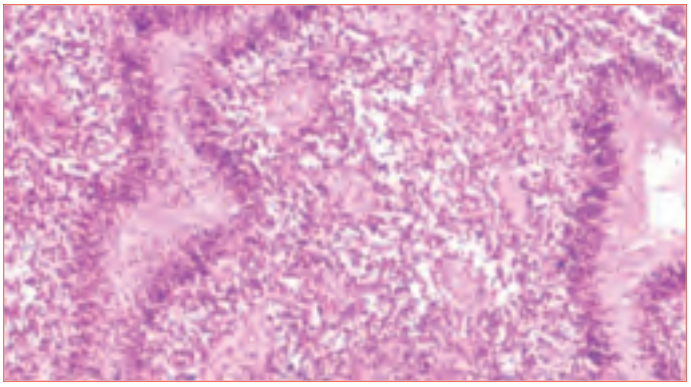
Strict Criteria for Recruitment

Dr. Lai is aiming to recruit up to 20 patients in the trial, but added that the study has strict inclusion and exclusion criteria. "It is by no means a very easy trial to get into—we're very vigilant in our screening of patients," she said. Patients are ineligible if they have undergone chemoradiation and still have a residual tumor of more than 1 cm square, or if they have more than one lesion.

"Timing issues are also important for entering this trial," said Dr. Lai.



This microscopic view shows a histologic specimen of glioblastoma — also called GBM, glioblastoma multiforme.

"The patient would have to be screened probably before they start chemoradiation or early during concomitant therapy to have a chance to get into the trial because the study starts two weeks after the completion of chemoradiation."

The major criterion is that patients must be EGFRvIII positive. "We previously thought up to 40 percent of patients express EGFRvIII," Dr. Lai explained. "The current estimate of about 25 percent is certainly lower than previously reported, but that is our experience now in this large clinical trial."

Patients in CDX-110 studies eventually had progressive disease. "When these patients underwent surgery, their tumor tissue no longer showed the expression of EGFRvIII," said Dr. Lai. "The vaccine is actually effective in targeting the EGFRvIII population. While patients do recur somewhere down the road, it seems like the vaccine has been able to postpone the recurrence until much later."

"If this approach is validated, vaccine therapy could be added on to the existing regimen of combined chemoradiation," said Dr. Schwartz. "The most important thing is that this trial really gives hope to a disease that doesn't have a lot of hope. We're working every day to try to improve the outcomes of patients with glioma, and this is just one of many avenues of investigation that we are pursuing at NewYork-Presbyterian Hospital."

Some patients who do recur after the CDX-110 trial may be eligible for another vaccine trial recently opened at NewYork-Presbyterian Hospital. Neurosurgeon Jeffrey Bruce, MD, at NewYork-Presbyterian/Columbia, has begun enrolling patients in a vaccine trial using a heat shock protein for patients with recurrent glioma.

The ACT III study is sponsored by Celldex Therapeutics Inc. of Phillipsburg, NJ.

Perspectives on the Failure of Remyelination in Multiple Sclerosis

Contributing faculty for this article: **Timothy Vartanian, PhD, MD**

A central question in multiple sclerosis (MS) is why remyelination is partial and ultimately fails. The consequences of this ultimate regenerative failure are enormous for the patient since myelin functions not only to provide the high resistance low capacitance structure necessary for saltatory conduction but also is an essential supportive structure for axons. In the prolonged absence of myelin, axons ultimately degenerate and disability is in reality due to the combined consequences of demyelination and axonal/neuronal loss. Thus, achieving remyelination in MS is an essential therapeutic goal because it would serve both to restore saltatory conduction and preserve axonal integrity.

In considering molecular pathways that might function to inhibit normal remyelination, we turned to danger theory.

Why does remyelination ultimately fail in MS? The failure of remyelination in MS could theoretically be the consequence of:

- a deficiency in the number of oligodendrocyte progenitor cells (OPCs)
- impaired recruitment of OPCs to lesions
- the absence of a pro-myelination signal
- the presence of inhibitory influences on OPCs and their remyelinating capacity

If we turn to what is known about the histopathology of MS, we gain some insights. For example it is interesting that MS lesions have an abundance of premyelinating oligodendrocytes that remain in an immature state in contact with axons, thus suggesting that failure of remyelination is at least in part due to loss of pro-myelination signals or presence of inhibitory signals, rather than the absence of an appropriate precursor cell. Although regenerative failure is the current rule rather than the exception in MS, it does not have to be inevitable.

In considering molecular pathways that might function to inhibit normal remyelination, we turned to danger theory and a family of receptors termed toll-like receptors (TLRs) that function in innate immunity.

TLRs likely serve the major function of transducing danger signals. They are a family of innate immune receptors that recognize a spectrum of protein, lipid-based, or nucleic acid motifs and in turn initiate inflammatory responses. Later observations have extended the function of TLRs in mammals from the realm of immunity to cellular development more generally.What we have found is a novel ligand-receptor pair that functions in oligodendrocytes to prevent cellular maturation to the stage of the remyelinating oligodendrocyte. The ligand is the glycosaminoglycan hyaluronan, and the receptor is toll-like receptor 2 (TLR2).

We are particularly interested in the function of TLRs in central nervous system development and disease, and reasoned the following:

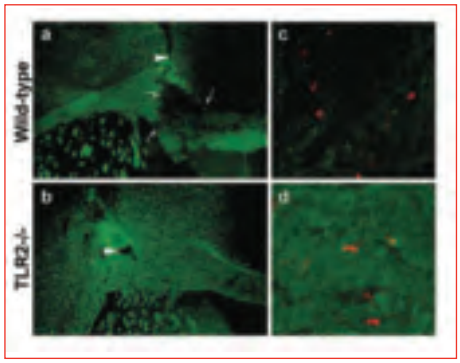
Oligodendrocytes in MS lesions express the danger receptor TLR2.

Since TLRs function to recognize danger signals and since the environment within an MS lesion is hostile to normal cells due to an abundance of inflammatory mediators and injured tissue, we reasoned that local danger signals in MS lesions may function to block the normal regenerative capacity of oligodendrocytes. We first examined the repertoire of TLRs expressed by oligodendrocytes and found abundant levels of TLR2. TLR2 was present in mouse oligodendrocytes *in vitro* and *in vivo*, but most importantly TLR2 was present in human oligodendrocytes in MS lesions.

Pathogen derived TLR2 agonists but not other TLR agonists block oligodendrocyte maturation.

Because of the abundance of TLR2 expression by OPCs, we tested whether known TLR2 agonists, including lipoteichoic acid, zymosan, and peptidoglycan, in addition to hyaluronan (HA), would have similar blocking effects on oligodendrocyte maturation *in vitro*. All TLR2 agonists blocked oligodendrocyte maturation while lipopolysaccharide and flagellin, TLR4 and TLR5 agonists, respectively, had no effect.

Recently, the glycosaminoglycan hyaluronan was identified within MS plaques and found to block oligodendrocyte maturation and remyelination in an MS animal model. Since hyaluronan may potentially function as an endogenous mammalian ligand for TLR2 and TLR4, we reasoned that TLRs expressed by oligodendrocyte progenitors may signal autonomously within these cells and hold oligodendrocyte progenitors in an immature state.



Hyaluronan blocks remyelination via a TLR2 dependent mechanism in an MS animal model. Brains of mice were injected with lysolecithin with or without 100 µg/ml hyaluronan. After 8d, brains were fixed, sectioned, and stained for MBP (green) (a and b). Hyaluronan blocked remyelination in wild-type mice but remyelination was more complete in TLR2 null mice. Staining for MBP (green) and olig2 (red), indicates that oligodendrocyte density is not appreciably different between lysolecithin-treated wild-type and TLR2 null mice (c and d).

Low molecular weight hyaluronan blocks oligodendrocyte maturation.

There is little known about the underlying mechanism by which HA blocks OPC maturation. Through *in vitro* studies, we found that HA blocks oligodendrocyte maturation directly in a dose-dependent manner. Our HA preparations were relatively free of contaminating proteins, DNA, or RNA that could account for the effects on oligodendrocyte maturation.

Loss of functional TLR2 restores normal remyelination in the lysolecithin model despite the presence of hyaluronan.

We utilized the lysolecithin MS model to study whether TLR2 is required for the previously characterized HA-mediated block in remyelination. First, we found that remyelination was approximately the same between wild-type and TLR2 null mice treated with lysolecithin only. We then confirmed that HA blocks remyelination in wild-type mice. In contrast, when lysolecithin and HA were injected into TLR2 null mice, we found normal remyelination, indicating that HA is unable to block remyelination in TLR2 null mice. Taken together, we have identified the receptor, TLR2, that mediates the repressive effects of HA on oligodendrocyte maturation *in vitro* and *in vivo*.

Magnesium Offers Neuroprotection During Carotid Endarterectomy

Contributing faculty for this article: **E. Sander Connolly, Jr., MD**

Laboratory and clinical studies have suggested that magnesium has neuroprotective effects. Columbia researchers at NewYork-Presbyterian Hospital, led by E. Sander Connolly, Jr., MD and Eric J. Heyer, MD, PhD, have shown for the first time that patients who received intravenous magnesium during carotid endarterectomy had better postoperative neuropsychometric function than those who received a placebo, indicating that this approach may reduce the risk of cognitive decline that can occur with this procedure. Their results were reported in the May 2009 issue of the *Journal of Neurosurgery*.

"Magnesium is a neuroprotective agent that is widely available, easy to give, on most hospitals' formularies, and safe," asserted study author Dr. Connolly, Associate Professor of Neurological Surgery at Columbia University College of Physicians and Surgeons, and Director of the Cerebrovascular Research Laboratory at NewYork-Presbyterian/Columbia. "If additional studies in a larger number of patients can confirm its use in this setting, it could become a new standard of care."

Magnesium's benefits may stem from its ability to protect neurons by blocking calcium channels. The IMAGES trial failed to show a benefit of giving magnesium within 12 hours of acute stroke, but the ongoing FAST-MAG study is assessing the potential value of giving magnesium to suspected stroke victims by paramedics within 120 minutes of the onset of ischemic symptoms.

About a quarter of patients undergoing carotid endarterectomy experience cognitive decline in the early postoperative period as a result of cerebral ischemia. The risk is higher in some groups, such as diabetics and patients with certain genetic mutations (such as aberrations in the *ApoE4* gene).

Assessing Cognitive Outcomes

In the current study, Dr. Connolly and his colleagues, including researchers from New York University Medical Center, examined neuropsychometric test (NPT) results among 92 patients undergoing carotid endarterectomy who received one of three intravenous doses of magnesium sulfate or a placebo during the procedure. The testing was performed before surgery and on postoperative Day 1.

Cognitive testing included the Boston Naming Test to assess verbal identification of objects; the Halstead-Reitan Trails Parts A and B to evaluate visual, conceptual, and visuomotor tracking; the Controlled Oral Word Association Test to measure verbal fluency; and the Copy Portion of Rey Complex Figure Test to assess visuospatial organization. Testing was performed more than three hours after administration of any analgesic or sedative medication.

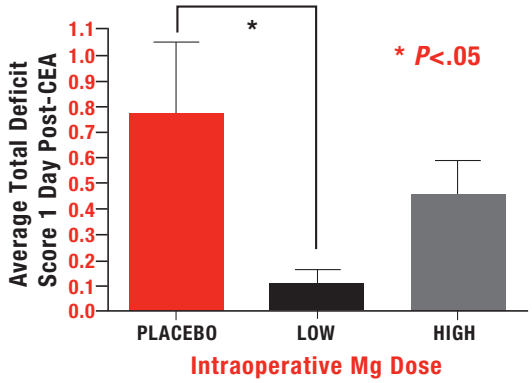
Compared with placebo, patients who received magnesium sulfate performed better on the neuropsychometric tests. Age and presence of diabetes had no impact on NPT results.

When examined by dose, patients who received a total of 10g or 18g of magnesium sulfate displayed better cognitive outcome than the placebo group, but no benefit was observed in the patients who received 20g of magnesium. Prior experience with magnesium suggests that high doses may induce hypotension and that substantially elevated serum magnesium levels impair cognitive ability.

Dr. Connolly noted that in most cases, the postoperative cognitive impairment associated with carotid endarterectomy does not significantly hamper daily quality of life. "However, any cognitive loss is not a good thing," he said. "In studies of large populations, it's been shown to be a strong predictor of death."

Magnesium Protocol Groups into which 92 patients were assigned

Group	No. of Patients	Magnesium Administered (g)		
		Loading Dose	At Infusion	Total Infused
placebo	43	0	0	0
Protocol I	13	2	8	10
Protocol II	7	2	16	18
Protocol III	29	4	16	20



Graph showing that patients who received lower doses of magnesium had significantly lower total deficit scores than patients in the placebo group ($P < 0.05$).

Halstead-Reitan Trails Part A and B and the Rey Complex Figure (right to left) are the backbone of the neuropsychometric battery, which also includes the Controlled Oral Word Association Test and the Boston Naming Test.

Other studies have touted the benefits of magnesium. Laboratory studies in rodents have shown that magnesium reduces infarct volume after the onset of cerebral ischemia. Magnesium administration may reduce gross motor dysfunction, mortality, and the rate of cerebral palsy in infants born to women at risk for preterm birth. And patients who received magnesium before cardiac surgery demonstrated improved postoperative neurological and neuropsychometric examinations.

Dr. Connolly and his colleagues are awaiting the results of the CREST trial this fall to see if stenting or endarterectomy will be recommended as the preferred approach for treating carotid atherosclerosis. If stenting is recommended, they may assess the benefits of magnesium infusion during this procedure. If endarterectomy is indicated as the preferred approach, the researchers will evaluate magnesium infusion in larger groups of patients undergoing this procedure.

Teen Depression Linked to Lack of Sleep

Contributing faculty for this article: **James E. Gangwisch, PhD**

The importance of sleep to human health is obvious, but the physiological processes that take place in our brains and bodies during sleep are not. In particular, a lack of sleep often precedes depression, but whether it is a cause of depression or simply a prodromal symptom has been a matter for debate. Columbia researchers in the Department of Psychiatry of NewYork-Presbyterian/Columbia University Medical Center recently concluded a study that provides new insight into the relationship. They presented their results at SLEEP 2009, the Associated Professional Sleep Societies annual conference.

The researchers used data from 15,659 subjects enrolled in the National Longitudinal Study of Adolescent Health (Add Health), a school-based, nationally representative, probability-based sample of U.S. adolescents in grades 7 to 12 in 1994-96. Through in-home interviews with adolescents and their parents, the Add Health study examined relationships between health-related behaviors, social contexts, and health outcomes in adolescence and young adulthood. As part of the study, parents were asked what time the adolescents had to go to bed on weeknights, while adolescents were asked about sleep duration, their perception of getting enough sleep, depression, and suicidal ideation.

"It's been known for a long time that short sleep duration precedes depression, but it is hard to show that lack of sleep can contribute to depression using epidemiological studies," said James E. Gangwisch, PhD, Assistant Professor of Psychiatry at Columbia University College of Physicians and Surgeons. "We approached this a little bit differently. We looked at parental mandated bedtimes as an actual risk factor for depression. We would presume that if the adolescent was depressed, they might have insomnia and it could affect what time they go to bed, but it shouldn't affect what time their parents tell them they have to go to bed."

The researchers found that adolescents whose parents set bedtimes of 12 midnight or later were 25 percent more likely to suffer from depression and 20 percent more likely to have suicidal ideation than adolescents with parental-set bedtimes of 10 pm or earlier. Their results provide new evidence that short sleep duration could play a role in the etiology of depression, and that earlier parental set bedtimes could protect against adolescent depression and suicidal ideation by lengthening sleep duration.

Throughout adolescence, there are significant physical, cognitive, emotional, and social changes that can impact sleep duration. Young adults develop a circadian phase delay and an increasing preference to go to sleep at later hours. At the same time, most U.S. school districts begin their school days progressively earlier as students transition from elementary to middle school and then from middle school to high school. Many other activities compete with sleep, such as television, cell phones, the internet, video games, and social activities. As children get older, parents are also less likely to set bedtimes. Some studies estimate that adolescents need 9 or more hours of sleep per night, but the average adolescent sleep duration was 7 hours and 53 minutes, the Add Health study showed.

Dr. Gangwisch's analysis of the data showed that depression and suicidal thoughts were associated not only with later parental set bedtimes, shorter sleep duration, and self-perception of not getting enough sleep, but

also with female sex, older age, and lower self-perception of how much parents care about them. African American subjects and those of other races/ethnicities were at greater risk for depression than Caucasian and Hispanic subjects. Caucasian subjects were more likely than African American, Hispanic, and other race/ethnicity subjects to have parental set bedtimes by 11 pm, the study showed.

Discussing the potential mechanisms by which lack of sleep causes depression and suicidal thoughts, Dr. Gangwisch noted sleep

Odds ratios (95% CI) for depression.

	Model 1	Model 2	Model 3	Model 4
Parental Set Bedtime On Weekday Nights				
10:00 PM or Earlier	1.00	1.00	1.00	1.00
By 11:00 PM	1.15 (0.94-1.40)	1.11 (0.89-1.39)	1.09 (0.87-1.38)	0.97 (0.76-1.23)
By or After 12:00/Midnight	1.42 (1.21-1.67)	1.27 (1.06-1.51)	1.24 (1.04-1.49)	1.06 (0.87-1.29)
Age		1.10 (1.05-1.16)	1.09 (1.03-1.14)	1.05 (1.00-1.11)
Female		2.79 (2.31-3.38)	2.94 (2.43-3.56)	2.71 (2.23-3.29)
Race/Ethnicity				
Caucasian		1.00	1.00	1.00
African-American		1.49 (1.25-1.78)	1.49 (1.25-1.79)	1.38 (1.14-1.68)
Hispanic		1.09 (0.79-1.49)	1.04 (0.76-1.43)	1.03 (0.74-1.43)
Other		1.64 (1.30-2.08)	1.57 (1.23-2.02)	1.51 (1.18-1.94)
Self-Perception of Parents Caring			0.47 (0.42-0.53)	0.50 (0.45-0.56)
Sleep Duration				
<= 5 Hours				1.80 (1.29-2.51)
6 Hours				1.31 (0.98-1.73)
7 Hours				1.18 (0.96-1.46)
8 Hours				1.00
9 Hours				1.16 (0.87-1.56)
=> 10 Hours				1.36 (0.97-1.90)
Enough Sleep				0.36 (0.29-0.45)

The table above shows the odds of suffering from depression. After adjusting for multiple covariates, parental set bedtimes by or after 12:00 (midnight) continued to be significantly associated with increased risk for depression (OR = 1.24, 95% CI 1.04-1.49). Consistent with sleep duration and perception of getting enough sleep acting as mediators of the relationship between parental set bedtimes and the risk for depression, the inclusion of sleep duration and getting enough sleep in Model 4 appreciably attenuated the association. The relationship between depression and sleep duration was u-shaped, with both short and long sleep durations being associated with depression. Subjects who reported getting enough sleep were significantly less likely to suffer from depression. These findings suggest that later parental set bedtimes contribute toward shorter sleep durations and perceptions of not getting enough sleep, which in turn are associated with depression and suicidal ideation. The results from this study provide new evidence to strengthen the argument that inadequate sleep could play a role in the etiology of depression. Earlier parental set bedtimes could therefore be protective against depression and suicidal ideation in adolescents.

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continued from Teen Depression, page 6

deprivation has been shown to diminish people's ability to cope with stressful life events, which are associated with depression. He discussed a Harvard Medical School and University of California, Berkeley fMRI study that showed a lack of sleep resulted in inappropriate modulation of human emotional brain responses to aversive stimuli. "The sleep-deprived participants exhibited a hyper-limbic response by the amygdala in response to exposure to increasingly negative picture stimuli."

The researchers also pointed out that moodiness resulting from insufficient sleep has been theorized to interfere with teenagers' abilities to cope with daily stresses and to impair their relationships with peers and adults. "Deteriorating relationships can lead to deficits in social support, while adverse and stressful life events have been shown to contribute to depression," they continued. Finally, insufficient sleep has been shown to have a negative impact on judgment, concentration, and impulse control, which could together contribute to suicidality. Treatment for sleep disorders in hospitalized youth significantly reduced aggressive and impulsive behaviors.

Adolescents in the Add Health study were asked to rate their feelings about how much their parents cared about them, and Dr. Gangwisch and colleagues included this information in their analysis. "We theorized that the relationships between parental set bedtime, depression and suicidal ideation could be partially mediated by the adolescents' perception of how much their parents cared about them, but when we included this variable in our multivariate models, the associations were only slightly attenuated," he said. "In other words, the analysis demonstrated that sleep duration, not parental nurturing, was the mediating variable. Kids whose parents had them go to bed earlier got more sleep, and getting more sleep was what was protective against depression and suicidal thought."

Educating adolescents and their parents about healthier sleep hygiene practices could serve as primary preventative measures against depression and suicidal ideation, Dr. Gangwisch pointed out. "Some basic sleep hygiene techniques can be really helpful," he said. "Try to maintain a regular bedtime, and sleep in a comfortable, dark, and quiet environment. Avoid caffeine before bedtime. Exercising helps, but not too soon before going to bed. These are mostly common sense things that we're all supposed to do that we often don't."

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After two years, significantly more patients in the intervention group than in the usual care group were receiving treatment (84.9-89 percent versus 49-62 percent, respectively). Patients in the intervention group experienced a 2.2-times greater decline in suicidal ideation over the 24-month study period.

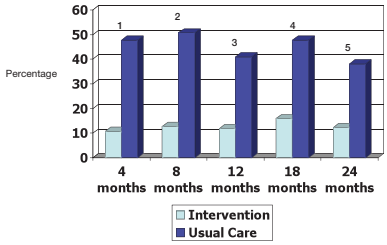
On average, patients in the intervention group responded to treatment sooner than those in the usual care group. Patients in the intervention arm continued to have a high response rate near the end of the follow-up period. From 18 to 24 months, 7.3 times more intervention patients responded to treatment than usual care patients.

Among patients with major depression, a greater number achieved remission in the intervention group than in the usual care group at 4 months (26.6 versus 15.2 percent), 8 months (36 versus 22.5 percent), and 24 months (45.4 versus 31.5 percent). Patients with minor depression demonstrated favorable outcomes regardless of treatment assignment.

"Depression is often inadequately treated because of a primary care physician's time constraints and a patient's reluctance to discuss symptoms and adhere to treatment," said Dr. Alexopoulos. "The critical finding of the PROSPECT study is that adding a trained care manager to primary care practices increases the number of depressed older patients who receive treatment and improves their outcomes—not only in the short term, but over two years. This is important, because depression can either become chronic or relapse after an initial improvement." Dr. Alexopoulos acknowledged that it may not be cost-effective for primary care physicians to add trained depression care managers in their individual offices. However, it would be feasible to train care managers in community-based counseling facilities to whom primary care physicians could refer their patients.

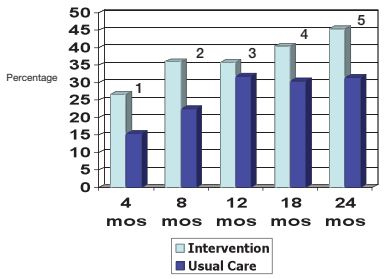
"This study shows that care managers can follow guidelines, are accepted by physicians, and are able to provide treatment for depression to a majority of patients who need it," said Dr. Alexopoulos. "Today our nation is focused on medical disease prevention as a way to improve the health of Americans and reduce healthcare costs. Reducing depression over long periods of time can be one of the ways to achieve these goals. Care management is relatively inexpensive; finding ways to reimburse it can make it broadly available and have a major impact on health care overall."

Percentages of Depressed Older Primary Care Patients Who Received No Antidepressant Treatment



1. Odds Ratio: 7.8, 95% CI: 4.9-12.6, 2=72.3, *P*<0.0001
2. Odds Ratio: 7.1, 95% CI: ,4.0-12.6 2=45.4, *P*<0.0001
3. Odds Ratio: 8.5, 95% CI: 4.7-15.4, 2=51.0, *P*<0.0001
4. Odds Ratio: 6.8, 95% CI: 3.7-12.6, 2=37.8, *P*<0.0001
5. Odds Ratio: 8.2, 95% CI: 4.5-15.2, 2=45.9, *P*<0.0001

Remission Rates (Hamilton scores<7) in Primary Care Patients with Major Depression



1. Odds Ratio: 3.1, 95% CI: 1.3-7.5, *P*<0.01
2. Odds Ratio: 2.9, 95% CI: 1.2-6.9, *P*<0.01
3. Odds Ratio: 1.3, 95% CI: 0.6-3.1, *P*<0.55
4. Odds Ratio: 2.0, 95% CI: 0.8-4.8, *P*<0.12
5. Odds Ratio: 2.9, 95% CI: 1.2-7.0, *P*<0.02