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## SECTION CONTENTS

815 Prevalence and Mental Health Treatment of Suicidal Ideation and Behavior Among College Students Aged 18–25 Years and Their Non–College-Attending Peers in the United States

825 Nocturnal Wakefulness Is Associated With Next-Day Suicidal Ideation in Major Depressive Disorder and Bipolar Disorder

832 Repeated Suicide Attempts and Suicide Among Individuals With a First Emergency Department Contact for Attempted Suicide: A Prospective, Nationwide, Danish Register-Based Study

## Online Exclusives:

e711 Clustering Suicide Attempters: Impulsive-Ambivalent, Well-Planned, or Frequent

e719 Rapid and Sustained Reductions in Current Suicidal Ideation Following Repeated Doses of Intravenous Ketamine: Secondary Analysis of an Open-Label Study

e726 Nocturnal Wakefulness as a Previously Unrecognized Risk Factor for Suicide

Visit  
PSYCHIATRIST.COM

Enter Keyword

For more information about

Online Exclusives

see page 789

## Subtyping Suicidal Behavior: A Strategy for Identifying Phenotypes That May More Tractably Yield Molecular Underpinnings

One might be inclined to view this month's Focus on Suicide section as covering 3 themes: nighttime wakefulness as a predictor of suicidal behavior, clinical features of suicidal behavior, and effects of interventions on future suicidal ideation or behavior. However, a strong current underlies all 6 articles: the notion that there may be subtypes of suicidal behavior with relevant clinical, pharmacologic, and biological implications.

Two articles focus on the role of insomnia in the development of suicide risk. Ballard and colleagues studied treatment-resistant mood-disordered individuals and found that wakefulness at 4:00 AM was associated with next-day suicidal ideation as measured by item 3 of the Hamilton Depression Rating Scale. This was so even after controlling for severity of depression. This observation comports well with Perlis and colleagues' study, which used information from the National Violent Death Reporting System and the American Time Use Survey, which tracks the proportion of the American population awake per hour across the 24-hour day. They found that suicides were 3.6 times more likely among those who are awake from 00:00 to 05:59 compared to the suicide rate observed between 06:00–23:59. The highest rate occurred during the 02:00–02:59 hour. That suicides are occurring at high rates per person awake during the night suggests that suicidal ideation is occurring during nighttime wakefulness, and not only the day following wakefulness. Thus, the next-day suicidal ideation observed by Ballard may reflect a continuation of ideation present the previous night as well. Rarely do clinicians investigate whether wakefulness at night is paired with suicidal ideation, but this may represent a unique subgroup of individuals at risk for suicide.

In the search for subcategories, Lopez-Castroman et al studied 1,009 hospitalized suicide attempters to identify clinically distinct clusters of suicidal individuals. Most individuals were in a cluster characterized by less lethal means and planning ("impulse-ambivalent"). A second cluster featured more carefully planned attempts ("well-planned"), with more alcohol or drug use before the attempt and more precautions to avoid interruptions. A small third cluster included individuals reporting more attempts ("frequent"), more often serious or violent attempts, and an earlier age at first attempt. This third cluster reported high levels of childhood abuse. Han et al used data from the 2008–2013 National Surveys on Drug Use and Health to compare the incidence of self-injurious behavior in 18- to 25-year-olds (N = 135,300) who attended college full-time with those who did not. Full-time college students were less likely to report a planned suicide attempt and perhaps less likely to belong to a group similar to Lopez-Castroman and colleagues' second cluster.

The effect of interventions was explored by Fedyszyn et al, who report that individuals evaluated in the emergency department (ED) after attempted suicide (N = 11,802) are at risk for both repeated suicide attempt (16%) and suicide (1.4%). Of note, the highest risk for repeated attempt was among those over 35 years, those with recent psychiatric treatment, and those seen in the ED after attempted hanging, strangling, or suffocation. These latter methods also predicted suicide, as did psychiatric hospitalization for the index attempt, suggesting that ED clinicians are appropriately identifying high-risk individuals. Risks for repeated attempt or suicide were highest in the first week after ED visits. In a separate study, Ionescu and colleagues examined pharmacologically treated outpatients with treatment-resistant MDD who had current, stable ( $\geq 3$  months) suicidal thoughts. They administered 6 open-label ketamine infusions over 3 weeks. Suicidal ideation was assessed at 240 minutes postinfusion and during a 3-month follow-up. During infusions, 7 of 14 patients (50%) showed remission of suicidal ideation, even when depression did

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not remit. Repeated doses of open-label ketamine rapidly and robustly decreased suicidal ideation, and this decrease was maintained for at least 3 months following the final ketamine infusion in 2 patients. These studies underscore the challenge faced in the clinic wherein even aggressively treated patients, either hospitalized or on robust pharmacologic treatment, continue to struggle with suicidal ideation and therefore remain at risk.

The findings from Ionescu et al and Fedyszyn et al underscore the imperative to identify pharmacologic and psychosocial interventions that specifically target suicidal behaviors and, as important, to determine what treatments are best for which patient(s). It stands to reason that as complex as suicidal behavior is, it most likely comprises several

different phenotypes. As long as we study suicidal behavior as a monolithic entity, our search for the pathophysiology of this behavior will be hampered, a critical problem since identification of the molecular architecture of this behavior is the most likely road to finding precise treatments. Delineation of subcategories may reveal suicide phenotypes that are more tractable in the search for molecular underpinnings, which may ultimately deliver precise treatments for the patients who need them most.

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