Editor's Note

Improving the Accelerated Pathway to Cancer Drug Approvals

The US Food and Drug Administration (FDA) must balance the need to bring potentially lifesaving drugs to market with the need to ensure the safety and effectiveness of these drugs. To balance these competing goals, the FDA has increasingly used the accelerated pathway, which is meant for drugs that treat serious conditions and fill an unmet medical need. Approval is based on a surrogate or an early clinical endpoint and is conditional on the completion of confirmatory trials, which are planned prior to the approval process.

Once granted, accelerated drug approvals are subject to withdrawal if "a postmarketing clinical study fails to verify clinical benefit."[1] The FDA defines *clinical benefit* as prolonging life or improving the quality of life (QoL). Withdrawal of approval is rare. The only drug for which the FDA withdrew approval—as a result of failure of confirmatory data—was bevacizumab for metastatic breast cancer in 2011. However, Medicare and other major insurers still cover bevacizumab for this indication, despite the FDA ruling or the drug's lack of clinical benefit.

In this issue of *JAMA Internal Medicine*, Rupp and Zuckerman[2] examine 18 cancer drugs that received accelerated FDA approval but were found in postmarketing confirmatory trials to have no overall survival (OS) benefit.[3] Less than half of these drugs had been studied using QoL outcomes. Although 6 drugs lack OS or QoL benefit, all but 1 (bevacizumab) have retained their approval and are still on the market.

We suggest 3 improvements to the accelerated pathway for cancer drug approvals. First, confirmatory postmarketing studies for accelerated drug approvals should include both OS and QoL outcomes because these are the 2 facets of clinical benefit currently being used by the FDA. Second, preapproved QoL measures should be published for specific drug classes. Third, anticipated or clinically significant changes in OS and in QoL measures should be defined a priori to facilitate the identification of drugs whose "postmarketing clinical study fails to verify clinical benefit."

In following the principle of "first, do no harm," the FDA should promptly withdraw approval for cancer drugs that are proven to have no clinical benefit. Removing these drugs, each of which costs between $20 000 and $170 000 per year, from the market will improve the quality and value of cancer care.

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Sleep Loss in the Homeless—An Additional Factor of Precariousness: Survey in a Group of Homeless People

Sleep is a key component of good health.[1] Sleeping less than 6 hours per night is associated with increased risk of obesity, type 2 diabetes, cardiovascular disease, depression, anxiety, pain, and accidents.[2] Being homeless makes sleep particularly difficult. Homeless facilities are often closed at night, and homeless people face inclement weather, darkness, and fear for their personal security. Owing to limited resources, many facilities limit the number of nights per individual. Thus, many homeless persons have no regular access to a safe and warm bed at night.

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Methods | This survey was approved by both the CNIS (Conseil national de l'information statistique) and the French National Institute for Demographic Studies (INED) ethics committee. Participants who agreed to participate were informed by interviewers at the moment of the survey, but written informed consent was not required by the committees for this epidemiological survey. To better characterize this problem, we collected information on sleep from a health survey conducted by the French National Institute on Statistics and Economic Studies and the INED.[3] We surveyed 3741 persons who met the definition of homeless (attending sites that offer free meals, associated with social and medical assistance services, and in French cities with more than 20 000 inhabitants). After excluding 288 incomplete questionnaires, we analyzed responses from 3453 individuals; 2068 men and 1385 women, with a mean age of 39.8 years. At the time of the survey, 197 respondents were living on the street, 447 were in collective short-term shelters (housing for <1 week), 1320 in collective long-term shelters (housing for >1 month), 240 in small social services paid hotels, and 1249 in individual facilities (1 or 2 bedrooms for homeless persons with children).

The questionnaire asked about total sleep time at night and over the 24 hours prior to the interview; insomnia defined by the *International Classification of Sleep Disorders, Third Edition*; whether drugs or alcohol were used to promote sleep, and whether the participant experienced frequent daytime fatigue. We compared homeless persons to age-, sex-, and location-matched controls enrolled in the 2010 National Health Barometer, a large representative survey of the French adult population that asked similar questions on sleep.[3]

Results | Homeless persons reported significantly shorter total sleep time than the general population (6 hours 31 minutes vs 7 hours 9 minutes) (**Table**). Among the homeless, 8% reported less than 4 hours of total sleep time over the past 24 hours compared with 3% of the general population; homeless women were twice as likely as men to report that they slept less than 4 hours. Insomnia was reported by 41% of homeless individuals compared with 19% of controls. Daytime sleep

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Table. Total Sleep Time, Complaints of Insomnia, and Use of Hypnotic Agents in 3453 Homeless Persons Compared With 3453 Controls[a]

Characteristic	All Homeless	Shelterless	Type of Shelter		Small Hotel Rooms	Individual Rooms in Long-term Shelters	Control Group	*P* Value[b]
			Short-term	Long-term				
Individuals, No.	3453	197	447	1320	240	1249	3453	
Total sleep time, minutes, mean (SD)	417 (7)	370 (25)	447 (28)	421 (6)	401 (11)	420 (13)	NA	
Night	391	340	423	390	371	404	429	<.001
Sleep per 24 h, h								
<4	8	22	8	8	6	5	3	<.001
4-5	8	8	8	7	5	10	4	.006
5-6	12	16	7	11	18	10	11	.32
6-7	17	16	17	16	22	17	23	.003
7-8	16	11	14	18	15	17	31	<.001
8-9	17	12	14	17	16	20	18	.62
9-10	8	3	10	9	8	7	6	.002
≥10	13	11	21	13	9	13	2	<.001
Experience insomnia, No.	41	45	38	42	37	42	19	<.001
Use of hypnotic agents, No.	25	15	20	31	15	28	15	<.001
Experience daytime fatigue, No.	33	38	39	30	36	32	15	<.001

[a] Age-, sex-, and location-matched persons in the general French population.

[b] Comparison between homeless individuals and controls.

duration averaged only 30 minutes per day, yet 33% of homeless persons complained of daytime fatigue compared with 15% of the general population. Among the homeless persons, 25% reported that they regularly took a drug to help them sleep vs 15% of controls.

Discussion | Our survey shows that in France, homeless people sleep less and are more likely to have insomnia and daytime fatigue than persons in the general population. Sleep is important for good health[1,2] and necessary to the ability to work and successfully perform daily activities. Improving the quality and duration of sleep in the homeless may, therefore, improve alertness, health, and the ability to face daily tasks.

We believe that improving sleep deserves more attention in this vulnerable group. We strongly support strategies other than hypnotic agents to improve sleep in the homeless, including more careful control of noise, lighting, heating, and air conditioning at night. Facilities could provide residents with sleep aids, such as earplugs, eye sleep masks, and pillows. Screens between beds could offer some sense of privacy, even in collective dormitories, and addressing issues of personal security should promote better sleep. Ideally, housing facilities would provide individual rooms, but collective shelters might be better organized with specific architecture and schedules to promote sleep.[4]

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Study concept and design: Leger, Beck.
Acquisition, analysis, or interpretation of data: All authors.
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Editor's Note

Sleeping on the Street

It seems that we increasingly walk by homeless people sleeping—or trying to sleep—on a cold sidewalk near the warmth of a heating vent. Even for those who secure a place in a shelter, it can be difficult to sleep in an unfamiliar, often crowded, and sometimes insecure place. Perhaps it's obvious that homeless people are more likely to have difficulty sleeping than people who sleep in their own homes. But given the importance of sleep for good physical and mental health, we think the work of Léger et al[1] in this issue of *JAMA Internal Medicine* in quantifying the prevalence of sleep problems in the homeless is important, and lays groundwork to start to address this problem. We recognize that the homeless population and homeless services are different in France than in the United States, but we believe that the magnitude of the problem of poor sleep is likely similar in homeless persons everywhere.

Deborah Grady, MD, MPH

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LESS IS MORE

Priority Levels in Medical Intensive Care at an Academic Public Hospital

Critical care services can be life-saving, but many patients admitted to intensive care units (ICUs) are too sick or, conversely, not sick enough to benefit.[1,2] Intensive care unit overutilization can produce more costly and invasive care without improving outcomes.[3,4] Guidelines from the Society of Critical Care Medicine (SCCM) prioritize patients for ICU admission based on projected likelihood of benefit (from highest to lowest priority) as follows[5]: priority 1: critically ill, needing intensive treatment and monitoring that cannot be provided outside of ICUs; priority 2: not critically ill, but requiring close monitoring and potentially immediate intervention; priority 3: critically ill, but reduced likelihood of recovery because of underlying diseases or severity of acute illness; and priority 4: not appropriate for ICU; equivalent outcomes achievable with non-ICU care based on low risk of clinical deterioration, presence of irreversible illness, or imminent death.

This study determined the proportion of medical ICU patients in each priority group within a tertiary care academic public hospital.

Methods | We prospectively studied all patients admitted to the medical ICU from July 1, 2015, to June 15, 2016 (n = 808). The study was approved as an exempt protocol by the institutional review board at Los Angeles Biomedical Research Institute. Medical records were reviewed by the ICU director (D.W.C.) each day. Reasons for ICU admission and ongoing ICU needs were evaluated and assigned priority ranks according to SCCM guidelines (priority 1-4). Because needs for ICU care may change, each ICU day was ranked using the same priority categories but adding a fifth category for patients awaiting transfer out of the ICU to examine the distribution of patient-days at each priority level. We categorized patients needing close monitoring but otherwise receiving care that could be provided outside of the ICU as priority 2, and patients with limited life expectancy or poor prospects for meaningful functional recovery as priority 3. When priority ranks were uncertain from medical record review, ICU physicians (attending or fellow) adjudicated (19.9% of cases). A random subsample of 80 medical records was re-reviewed by a coinvestigator (D.D.) blinded to the study hypothesis and priority ranks assigned; concordance in priority ranks was 85.0%.

Results | Of 808 medical ICU admissions, 46.9% were categorized as priority 1, 23.4% as priority 2, 20.9% as priority 3, and 8.8% as priority 4 (Table). Patient characteristics, comorbidities, severity of illness, and primary ICU diagnoses are shown in the **Table**. Intensive care unit and hospital mortality rates were 13.4% and 19.6%, respectively, for priority 1, 4.2% and 10.6% for priority 2, 47.3% and 61.9% for priority 3, and 2.8% and 7.0% for priority 4 (Table); 56.0% of priority 1 patients and 62.4% of priority 2 patients were discharged home compared with 6.0% of priority 3 patients (Table). Of 3794 patient-days, 35.2% were assigned priority 1; 25.3%, priority 2; 27.5%, priority 3; 3.3%, priority 4; and 8.7%, priority 5.

Discussion | Over 50% of patients admitted to the ICU had priority ranks suggesting that they were potentially either too well (priority 2) or too sick (priority 3) to benefit from ICU care or could have received equivalent care in non-ICU settings (priority 4). Nearly 65% of total ICU days were allocated to care that was considered discretionary monitoring (priority 2), low likelihood of benefit despite critically illness (priority 3), or manageable in non-ICU settings (priority 4 and 5). Our findings suggest that ICU care is inefficient, devoting substantial resources to patients less likely to benefit.[6] Determining appropriateness of ICU care is complex; in addition to expected benefit, it must incorporate patient preferences, availability of ICU resources, and levels of medical complexity manageable in non-ICU settings. As such, our study cannot fully differentiate between appropriate and inappropriate care. However, appropriateness of ICU care for patients previously in good health but with poor prognoses from acute illness is likely different than those whose expected benefit from ICU care is low from progressive irreversible medical comorbidities. In our study, 26.0% of priority 3 patients had advanced malignant neoplasms and 27.2% had advanced dementia, suggesting that many patients in this priority group were at risk for receiving inappropriate ICU care. This was a single-hospital study; results may differ at other institutions. However, categorizing ICU admissions by priority ranks identified opportunities to improve allocation of ICU resources at our institution. Other hospitals could use this approach to improve the efficiency of their ICU utilization.

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