Speed of Psychosis Progression in People at Ultra-High Clinical Risk: A Complementary Meta-analysis

The transition to psychosis in patients at ultra-high clinical risk (UHR; as defined elsewhere) is most likely to occur within the first 2 years after presentation to clinical services (risk estimate, 29%; 95% CI, 23-36). After this phase, the speed of psychosis progression tends to plateau from the third year, reaching approximately 35% after 10 years. However, the exact speed of psychosis progression at a particular point during the critical first 2 years is unclear, preventing clinical advancements in the field.

Methods | We used the pooled cumulative transition curve from our previous meta-analysis; survival curves from 6 independent studies (n = 1327) covering 24 months were digitally measured and statistically combined. The gradient of the cumulative curve was calculated to determine the speed of psychosis progression in UHR individuals. The chance of transition over a given month after presentation (Figure 1) and the cumulative chance of transition given transition occurs by 2 years (Figure 2) were modeled using an exponential regression model; we selected this model because it ensured the probability of transition remained finite at zero months and greater than zero at all future points.

Results | The gradient of the smoothed combined cumulative transition is shown in Figure 1. It indexes the speed of psychosis progression in a UHR sample, showing the probability of transition to psychosis in any given month after presentation. Figure 2 shows the cumulative probability of transition within the subgroup of UHR patients who will transition to psychosis in the first 2 years.

Discussion | The speed of psychosis progression in UHR people is greatest during the first months after presentation. Half of UHR people who progress to psychosis within 2 years will do so within the first 8 months since presentation to high-risk services. These findings are important, particularly because the duration of the UHR state is known to impact clinical outcomes and underlying neurobiology. First, they can be used to directly inform clinicians of the risk for psychosis in a UHR patient (eg, the risk for transition between monthly meetings with a psychologist at 12 months since first presentation can be determined from Figure 1 as approximately 1%). Second, given that cognitive behavioral therapy is the recommended and most effective focused intervention for UHR individuals, such treatment should be offered on a weekly basis, at least during the first 8 months since presentation to the high-risk service. It seems relevant to reduce the waiting list time to start the treatment and to offer close-in weekly monitoring to UHR patients who refuse the psychological intervention. There are also some diagnostic implications for the responsible clinicians. Our finding that the speed of psychosis transition is highest in the...
first month (2%) raises the possibility that some patients may have already been psychotic but underreporting at the time of the initial assessment.7 High-risk services should place more emphasis in conducting a prolonged and ongoing careful assessment to rule out concealed psychotic symptoms. Diagnostic skepticism should be considered when treating UHR patients included on the basis of brief limited intermittent psychotic symptoms, which is already clinically closer to the psychosis threshold. A 2-step approach—excluding patients who had reported meeting the UHR criteria at first baseline assessment but disclosed overthreshold psychotic experiences consistent with transition at a second assessment conducted in the first month—could be adopted.7 Finally, the current results may inform the planning and development of research studies in UHR individuals (eg, power calculations). For example, future neuroimaging studies may want to plan sequential scans in the first months to better clarify the dynamic neurobiological processes underlying the onset of psychosis in UHR individuals.

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COMMENT & RESPONSE

The Popularity of Benzodiazepines, Their Advantages, and Inadequate Pharmacological Alternatives

To the Editor—In an article, Olfson et al1 reported higher rates of long-term benzodiazepine use among older adults in the United States. They assumed that benzodiazepines are prescribed to older individuals mainly for insomnia and anxiety and stated alarmingly that “most physicians do not view continuous use of benzodiazepines by older adults as a public health problem.”

Is long-term benzodiazepine use by older adults really a public health problem? Before rushing to respond affirmatively, it would be useful to reconsider a number of negative notions about benzodiazepines that have not received unequivocal empirical support. For example, hip fracture rates in the elderly population were not found to be necessarily associated with benzodiazepine use2 and the effectiveness of benzodiazepines during long-term treatment of anxiety disorders usually does not diminish over time.3 Benzodiazepines remain popular because of their consistent and reliable effectiveness against many symptoms of anxiety, relatively good tolerability, quick onset of action, and possibility of use on an as-needed basis. Furthermore, alternative medications, such as antidepressants, have not been as useful for anxiety disorders as they had initially seemed to be.

Indeed, prescribers’ choice of benzodiazepines may also be owing to inadequate pharmacological alternatives for long-term treatment of insomnia and anxiety. Olfson et al4 discussed the limitations of alternative hypnotic agents, such as zolpidem, but they hardly mentioned problems with commonly prescribed antidepressants. For example, adverse effects occurring in the course of long-term treatment with selective serotonin reuptake inhibitors include hyponatremia, sleep disturbance, suicidal ideation, osteoporosis with the risk for fractures, sexual dysfunction, upper gastrointestinal bleeding, cardiovascular abnormalities, extrapyramidal symptoms, apathy, and weight gain.4 These adverse effects, in addition to the potential for drug interactions with certain selective serotonin reuptake inhibitors and discontinuation problems, have led to a suggestion that benzodiazepines are much safer than antidepressants in the long-term treatment of anxiety disorders.5