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Duration and Relevance of Untreated Psychiatric Disorders, I: Psychotic Disorders

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The association between longer duration of untreated psychosis (DUP) and poorer outcomes in first episode psychosis (FEP) was first observed over 3 decades ago¹ and has been consistently replicated since.^{2–4} Recently published results from the National Institute of Mental Health–sponsored Recovery After an Initial Schizophrenia Episode Early Treatment Program study (RAISE-ETP) indicated that the median DUP in patients enrolled from 34 community mental health across 21 US states was 74 weeks, confirming that patients with less than the median DUP benefited significantly more from the coordinated specialty care that RAISE-ETP investigated compared to community care.⁵ This median 18-month delay to antipsychotic treatment despite full psychosis seems inordinate 3 decades after it was first described as a predictor of poor outcomes. Although the causality of this association is likely complex and the issue of causality has remained controversial,^{2–4} the time lag between the onset of psychotic symptoms and initiation of evidence-based treatment should in any case be minimized to reduce the burden and risk of untreated psychiatric symptoms. Prompted by the disconcerting finding of long DUP in young people with FEP in the United States, this first of a series of 2 ASCP Corner articles reviews the current state of DUP in patients with psychotic disorders.

ASSESSMENT AND DISTRIBUTION OF DUP

Determining accurately the time between first onset of the illness and its treatment or the DUP (time between onset of psychosis and its treatment) is challenging. Patients' initial psychotic experiences are diverse and nonspecific, may lie on a continuum with nonpathologic phenomena, and upon presentation have poor positive predictive value.⁶ This dimensionality complicates the categorical determination of the illness onset when judged retrospectively. Additionally, there is no consensus about what constitutes "treatment onset," with definitions ranging from first mental health provider contact to first adequate antipsychotic trial. Finally, the method of eliciting the information (clinical chart, structured assessment, etc) varies greatly and may yield different results. This variability in the criteria and methods used for measuring DUP could explain the heterogeneity of DUP across different studies and settings. Nevertheless, generally, the measurement of DUP has proven to have good to excellent interrater reliability.⁷ Therefore, although heterogeneous definitions of DUP can complicate comparing DUP across studies, measurements are reliable within the same study. Consistently, DUP varies widely across patients, with a strong right skewedness, in that there are outliers of very long DUP.^{2–4} Therefore, the median (ie, the duration around which equal numbers of people have higher or lower DUP) is preferred to describe the DUP distribution, although the mean is

often used, particularly in meta-analyses, as it is more easily pooled across studies.

CHARACTERISTICS AND CORRELATES OF DUP

Unlike for mental disorders with greater incidence in the general population for which data from clinical services utilization surveys exist,⁸ the lack of representative epidemiologic data on duration of untreated illness and DUP in FEP is a major limitation. Hence, most data are derived from clinical studies, with RAISE-ETP having reasonable external validity in the United States.⁵ In RAISE-ETP, a DUP longer than the median was related to greater positive and total symptoms severity, comorbid substance use, and lack of hospitalization prior to enrollment, while no association was found with sociodemographic variables.⁵ While these data shed light on the characteristics associated with longer DUP, they should be put in perspective with other results from clinical studies. For example, in inpatient FEP patients, longer DUP was associated with greater negative symptoms and lower insight and overall functioning at baseline.⁹ Although these associations are informative, systematic knowledge of correlates of longer DUP is lacking, which could help identify populations at risk, potential intervention targets, and fluctuations over time and across different geographical regions and allow monitoring of outcomes of much-needed interventions to shorten DUP.¹⁰ The wide range in DUP between cases (RAISE-ETP: 1–1,456 weeks) suggests that some factors may have powerful effects in delaying the onset of treatment, and their characterization is critical. Standardization of measuring and reporting of DUP in clinical studies is essential, given strong reliance on clinical studies as opposed to epidemiologic surveillance.⁸

IMPACT OF DUP

Meta-analytic studies have consistently found significant correlation coefficients between longer DUP and worse psychopathology at follow-up. Correlation coefficients were 0.28–0.29 at 6–12 months for total psychopathology and 0.19–0.28 at 1–2 years for decreased global functioning, which indicates small to medium sized associations.^{2–4} Even at ≥ 2 years follow-up, a meta-analysis still found significant correlation coefficients between longer DUP and total psychopathology (0.15) and global outcome (0.17),⁴ suggesting that these associations persist at least during the first several years of the illness. Therefore, if this association is causal, programs reducing DUP would have public health value through modification of the illness course. However, observational studies examining the role of possible confounders found that earlier age of symptom onset, more negative symptoms, later treatment onset, worse premorbid functioning and psychosocial support, or lower educational and socioeconomic status mediated the association between longer DUP and poorer outcomes.² Nevertheless, after adjusting each study included in one of the meta-analyses for these potential confounders, DUP remained an independent predictor of poorer treatment response, although the strength of the relationship varied.² However, this finding requires confirmation in samples in which DUP was reduced experimentally. Additionally, other downstream effects of shorter DUP, including potential beneficial effects on attitudes toward and engagement with mental health care, should be explored.

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J Clin Psychiatry 2017;78(3):358–359

<https://doi.org/10.4088/JCP.17ac11479>

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REDUCING DUP

Given its potential impact, research on strategies to shorten DUP, for example by understanding better pathways to care, is important. For instance, a meta-analysis identified that for the studies conducted in the United States, about half of the first contacts with a provider were made through emergency services.¹¹ The frequent utilization of emergency services for the first treatment encounter for symptoms that have often been present for months to years contrasts with the need to reach these patients before an emergency situation. Here, leveraging social media may be a promising approach beyond general educational campaigns and reduction of barriers to care.¹² Research involving technology-based interventions to reduce DUP will have to resolve ethical conflicts about privacy and identify consistent and specific markers within social media use changes associated with emerging psychosis.¹² This research should build on lessons learned from previous interventions conducted to reduce DUP. Mental health literacy campaigns combined with easily accessible and proactive early detection teams have reduced DUP in some studies.¹⁰ For instance, the early Treatment and Intervention in Psychosis (TIPS) study in Scandinavia showed that such campaigns reduced the median DUP from 16 to 5 weeks, which bounced back to 15 weeks after the program was discontinued, with similar results in the Early Psychosis Intervention Programme project in Singapore.¹³ However, neither the Early Psychosis Prevention and Intervention Centre service in Australia nor the Prevention and Early Intervention Program for Psychoses program in Canada successfully reduced DUP, which may be related to health care system-inherent differences.¹³ Nevertheless, the 18-month DUP found in RAISE-ETP calls for the development of interventions that target this public health problem effectively by addressing local barriers to care, ranging from lack of information to financial barriers to public view of psychiatric symptoms and stigma.¹⁴

In 2014, US President Obama signed into law the Consolidated Appropriations Act (www.congress.gov/bill/113th-congress/house-bill/3547), which provided approximately \$25 million for the Substance Abuse and Mental Health Services Administration's Mental Health Block Grant to support work reducing the delay between symptom onset and receipt of evidence-based interventions. The allocation of these resources was supported by previous evidence from multicomponent FEP treatment programs that were effective in Canada, Australia, and the United Kingdom (Senate Report 113-71¹⁵). This money is to be allocated for coordinated specialty care projects (CSC), which include psychopharmacologic treatment, supported employment and education, psychotherapy, case management, and family education and support, aiming to improve functional outcomes in individuals with FEP. While RAISE-ETP proved that CSC is effective in improving functional outcomes in real-world settings, CSC per design does not target explicitly the reduction of DUP, and in fact both CSC and treatment as usual did not differ in DUP at baseline.¹⁶ Therefore, initiatives, such as the Specialized Treatment Early in Psychosis—Early Detection (STEP-ED) project,¹⁷ which currently investigates whether the strategy that worked in the TIPS study in Scandinavia also reduces DUP and improves outcomes in the United States, are important. Given health care system disparities, such transcultural validation of the efficacy and cost-effectiveness of these programs,¹⁸ or subsequent strategic modification, is critical. Moreover, research is needed to investigate possible biological and nonbiological mechanisms by which reducing DUP would improve outcomes, including potentially reducing risk of harm to self or others.¹²

CONCLUSION

In summary, contemporary DUP, assessed in an effectiveness trial across 21 states in the United States,² proved to be inordinately long. Reasons to urgently target reducing DUP include the burden

and risk of untreated psychiatric symptoms and a potential effect on improving outcomes of psychotic illness, as longer DUP has consistently been associated with poorer outcomes. However, research on DUP is challenged by the reliance on data derived from clinical studies, which have questionable external validity and are difficult to compare with each other. Measuring and reporting DUP in ways that allow for comparison between studies is crucial to monitor the effects of interventions to reduce DUP across time and settings. Further, current interventions, such as those driven by the Consolidated Appropriations Act, as well as future research involving technology, should build on lessons learned from other interventions developed at the population level. A multidisciplinary collaboration between epidemiology, clinical services and implementation research, social scientists, informatics, patients and families, and other stakeholders is crucial for the effective development and monitoring of these interventions in the real world. Finally, research will have to clarify if shortening DUP in people with otherwise long DUP will significantly affect outcome or whether, and in whom, DUP is only a proxy for other clinical or biological variables that are truly driving the poorer outcome.

Potential conflicts of interest: Dr Correll has been a consultant and/or advisor to or has received honoraria from Alkermes, Forum, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, Lundbeck, Medavante, Medscape, Otsuka, Pfizer, ProPhase, Sunovion, Supernus, Takeda, and Teva; has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka; served on a Data Safety Monitoring Board for Lundbeck and Pfizer; and received grant support from Takeda. Dr Rubio has nothing to disclose.

Funding/support: Supported in parts by The Zucker Hillside Hospital and the National Institute of Mental Health Advanced Center for Intervention and Services Research for the Study of Schizophrenia grant MH 074543-01.

Role of the sponsor: The funding sources had no role in the planning or writing of this article.

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