interpersonal therapy. Although there is ongoing debate regarding whether non-specific versus specific factors make psychotherapy effective, there is an increasing focus on making psychotherapy more precise and personalised. Interpersonal therapy might inherently do this through its focus on here-and-now patient-specific factors that perpetuate depressive symptoms in adolescents (eg, grief and loss, role disputes and transitions, and interpersonal deficits) and might offer a true advantage over CBT.

At this juncture, few new paediatric pharmacotherapy studies are being done, except as regulatory agencies compel them. Innovations in psychotherapy are modest and focus largely on expanding delivery options and optimising efficiency.[10] The accelerating rate at which we meta-analyse these studies and the decelerating rate of new well-controlled clinical trials in young people creates a precarious imbalance in evidence-based medicine. Meta-analysing existing data is no substitute for new and innovative intervention studies in improving outcomes in child and adolescent psychiatry. Network meta-analyses like the one by Zhou and colleagues have value in helping clinicians compare treatments. However, they might increase the risk that clinicians and policy makers misinterpret them as narrowing treatment choices and obscuring the nuance that is crucial to interpreting and contextualising findings from individual trials. It is quite likely that a properly assessed child or adolescent with depression who is well-matched to an SSRI and any evidence-based, flexible psychotherapy will do well.

JRS has received research support from the National Institutes of Health (National Institute of Mental Health, National Institute of Environmental Health Sciences, and Eunice Kennedy Shriver National Institute of Child Health and Human Development) and Allergan, Neuronetics, and Otsuka. He has received material support from and provided consultation to Myriad Genetics and receives royalties from the publication of two texts (Springer) and serves as an author for *UpToDate* and an Associate Editor for *Current Psychiatry*. JRS also receives research support from the Yung Family Foundation. JTW has received royalties from Guilford Press and Oxford University Press for books published about Tourette's syndrome and from Wolters Kluwer for continuing medical education activity on childhood anxiety. He has served as an unpaid advisor to the Anxiety Disorders Association of America and the Trichotillomania Learning Center and an unpaid Director on the Board of Directors of the Tourette Association of American. He has served as a paid speaker for the American Academy of Child and Adolescent Psychiatry, the American Psychiatric Association, and American Academy of Pediatrics.

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Treatment delay in early psychosis: not a linear problem

See **Articles** page 602

Any illness, if left untreated, can become more complicated to treat. Psychosis is no exception. This should make early intervention in psychosis a pragmatic call with no prima facie argument against it. Reduction in the duration of untreated psychosis (DUP) underpins the rationale behind early detection and intervention in psychosis. Nevertheless, this very ethos of early intervention has come under scrutiny in the past decade. For example, a meta-analysis of longitudinal observational studies found that longer DUP was not a moderator of remission or recovery rates in first-episode psychosis.[1] More recently, Jonas and colleagues explored several explanatory models of this relationship.[2] They concluded that the apparent relationship between long


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DUP and poor prognosis is probably a spurious artifact of "lead time bias", resulting from individuals with a long DUP simply being further along the trajectory of their illness than those with shorter DUP.

Where experimental manipulation is not possible, verified models are needed that can explain the link between potential modifiable factors, such as DUP, and outcomes of clinical importance, to justify allocating resources to modify these factors.[3] In *The Lancet Psychiatry*, Richard Drake and colleagues use advanced statistical techniques on a large dataset of 948 patients presenting with first-episode psychosis (NEDEN) to explore the relationship between DUP and psychotic symptomatology at baseline, at 6 months and at 1 year.[4] Crucially, they replicate the initial findings in an independent dataset of 332 patients (Outlook). They compare several explanatory models and draw three significant conclusions. First, they found that the relationship between DUP and symptom improvement over 1 year was curvilinear. In other words, treatment delay was associated with progressively worse treatment response, but this response worsened more slowly and eventually plateaued as DUP lengthened. Second, long DUP was not associated with symptom severity at baseline in patients assessed within 3 weeks of presentation to services but predicted poor treatment response subsequently. Drake and colleagues suggest that this was probably because greater symptom severity led to a faster presentation ("confounded presentation"), thereby obscuring the relationship between DUP and baseline symptom severity. The only exception to this was depression; longer DUP was associated with both greater baseline severity and reduced treatment responsiveness (in the NEDEN cohort). Finally, they observe generality in the relationship between DUP and treatment responsiveness: all the symptom domains of psychosis respond poorly with delayed treatment. Unlike most other symptom domains of psychosis, most guidelines for psychotic disorders recommend therapeutic abstention for depression until acute psychotic symptoms resolve with treatment.[5] Although not an interventional study, Drake and colleagues' work indicates that depression might accumulate over the early phase of psychosis, highlighting the need to consider depression as a key treatment target for early intervention.

Drake and colleagues argue that treatment delay worsens profound underlying illness processes, of which we know very little. But this work gives us a vital clue. The authors observe that longer DUP does not predict baseline illness severity in patients assessed soon after presentation, but predicts the severity at follow-up. In this context, it is possible that treatment delay affects the processes underlying treatment responsiveness, rather than symptom formation per se. This interpretation seems more credible than the conventional, but often disputed, neurotoxicity argument that can reduce to toxic symptoms beget more toxic symptoms.[6] The novel insight from Drake and colleagues' work shifts the neurobiological focus of early intervention from distal changes that precede psychosis to changes more proximal to the psychotic episode, influencing its resolution. Mechanistically, prolonged untreated psychosis—and the associated excitatory drive—might invoke processes that deplete glutathione, an antioxidant, thereby reducing responsiveness to treatment. Low levels of glutathione have been shown to be a marker of late response to antipsychotics.[7] Another candidate marker is the functional connectivity of the triple network system, in particular the default mode network. Default mode network hypoconnectivity appears to mediate the relationship between long DUP and treatment response.[8] Untreated psychosis might invoke large-scale synaptic reorganisation characterised by hypo-connectivity; such a hypoconnected state might be suboptimal for antipsychotic drug response.[9]

Drake and colleagues' findings have several implications. First, studies that use predictive modelling for individualised outcomes could benefit from including variables that capture the nuanced theoretical relationships reported by Drake and colleagues.[4,10] Second, the curvilinear relationship between DUP and treatment success in early stages of psychosis strengthens the argument for more proactive early assessment and intervention that will shorten treatment delay. It would be best to cut the curve short, so we do not see the long tail of extreme treatment delays in future clinical samples. Equally crucial is to look for means to reduce the initial gradient of this curve, so that brisk treatment response is achieved irrespective of the DUP; this involves understanding and improving the processes underlying treatment response. A flatter slope

will mean latecomers to treatment are not penalised with a refractory illness. As we have learnt over the past two decades, even punctual treatment when symptoms first arise continues to be too late when it comes to psychosis.

LP reports grants and personal fees from Janssen Canada and Otsuka Canada, grants from Sunovion, and personal fees from SPMM Course UK and The Canadian Psychiatric Association, outside of the submitted work. RK declares no competing interests.

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What can psychiatrists learn from SARS and MERS outbreaks?

While standard care for patients with psychiatric disorders must continue during the current COVID-19 pandemic, psychiatrists also need to treat psychiatric complications of patients with this new disease. An estimation of expected prevalences of psychiatric disorders occurring in this group would help to redistribute mental health personnel between old and new tasks to serve the needs of both groups optimally. In *The Lancet Psychiatry*, Jonathan Rogers and colleagues[1] report the results of their systematic review and meta-analysis of psychiatric sequelae in patients admitted to hospital with severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 in the acute and post-illness stages of disease. The systematic review showed that most patients with SARS or MERS do not develop psychiatric disorders, but a significant minority exhibits confusion (36 [27·9%; 95% CI 20·5–36·0] of 129 patients), depressed mood (42 [32·6%; 24·7–40·9] of 129), anxiety (46 [35·7%; 27·6–44·2] of 129), impaired memory (44 [34·1%; 26·2–42·5] of 129), and insomnia (54 [41·9%; 22·5–50·5] of 129). The meta-analysis showed that the point prevalence in the post-illness stage was 32·2% (95% CI 23·7–42·0) for post-traumatic stress disorder, 14·9% (12·1–18·2) for depression, and 14·8% (11·1–19·4) for anxiety.

As the COVID-19 pandemic is so recent and ongoing, few studies reported on psychiatric disorders complicating this particular disease and those that did reported only short-term aspects. Rogers and colleagues circumvented this knowledge gap by taking together the few studies on psychiatric disorders in patients with COVID-19 with the much larger body of literature on psychiatric disorders accompanying two previous coronavirus epidemics: the 2002 SARS and the 2012 MERS outbreaks. From a biological perspective, it makes sense to merge data on SARS coronavirus 2 (SARS-CoV-2), which causes COVID-19, infections with those of SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV) infections because resemblance between these three types of coronaviruses is high.[2] SARS-CoV-2 is structurally and genetically highly homologous to MERS-CoV (>50% similarity) and SARS-CoV (>79% similarity).[3] Even the spike proteins that SARS-CoV and SARS-CoV-2 use to attach to the target cell membrane (spike protein S, which interacts with the angiotensin-converting enzyme 2 receptor) are


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Published **Online** May 18, 2020 https://doi.org/10.1016/S2215-0366(20)30219-4

See **Articles** page 611