Authors and Disclosures

Interviewer

Stephen M. Strakowski, MD

Chairman, Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine; Chief of Psychiatry, University Hospital, Cincinnati, Ohio

Disclosure: Stephen M. Strakowski, MD, has disclosed the following relevant financial relationships:
Served as a consultant for: Pfizer Inc.
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Chaired Symposium for: Consensus Medical Communications

Interviewees

Patrick McGorry, MD, PhD

Professor of Youth Mental Health, University of Melbourne; Clinical Director, Orygen Youth Health Research Center, Parkville, Victoria, Australia

Disclosure: Patrick McGorry, MD, PhD, has disclosed the following relevant financial relationships:
Received research grants from: Janssen; Cilar; AstraZeneca Pharmaceuticals, LP
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Rabindra Tambyraja, MD

Assistant Professor, Department of Psychiatry, University of Minnesota Medical School, Minneapolis, Minnesota

Disclosure: Rabindra Tambyraja, MD, has disclosed no relevant financial relationships.

Charles Schulz, MD

Professor and Head, Department of Psychiatry, University of Minnesota Medical School, Minneapolis, Minnesota

Disclosure: Charles Schulz, MD, has disclosed the following relevant financial relationships:
Served as a director, officer, partner, employee, advisor, consultant, or trustee for: Eli Lilly and Company; Biovail Corporation
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Alison Yung, MD

Professor, University of Melbourne; Staff Physician, Orygen Youth Health Center, Parkville, Victoria, Australia

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Should Schizophrenia Prodrome Be Treated?

Stephen M. Strakowski, MD; Patrick McGorry, MD, PhD; Rabindra Tambyraja, MD; Charles Schulz, MD; Alison Yung, MD

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Editor's Note:

Medscape recently invited Dr. Stephen Strakowski to moderate a virtual discussion between Drs. Patrick McGorry, Charles Schulz, Alison Yung, and Rabindra Tambyraja, MD on recognizing and managing patients at risk for schizophrenia. What follows is a transcript of their discussion.

Schizophrenia Prodrome: Introduction

Stephen M. Strakowski, MD: Has our field advanced enough that we can recognize 'at-risk' schizophrenia before its onset and prevent it with treatment? Is there a role for treatment in the so-called prodrome?

Patrick McGorry, MD: I certainly think so but the reservations stem from the fact that in the United States, treatment is equated with medication, and in this case antipsychotics. Other psychosocial and more benign interventions have such little respect. Is this too harsh?

Dr. Strakowski: I hate to think that the United States is so one-dimensional; on the other hand, the television show "Survivor" has been running for years now, so maybe we are!

Dr. McGorry: We have ["Survivor"] here too!

Dr. Strakowski: Drs. Schulz and Tambyraja - what do you think?

Rabindra Tambyraja, MD: I would hazard a guess that some of the over-reliance on medication and skepticism toward psychosocial interventions stems from a belief that psychotic disorders are "worse" than mood or anxiety disorders, and therefore require more "serious" treatments. Hopefully, my quotes show my thoughts about dismissing psychosocial treatments. There is evidence that high-conflict environments can be associated with a faster progression of psychosis, so it's a worthy hypothesis that decreasing the conflict and increasing the strength of psychosocial support could have a positive effect.

Also, if we're thinking of the prodrome as an earlier stage of illness, then there's no reason to think that the best treatments for full-blown schizophrenia are necessarily the best treatments for the prodrome. There has been very encouraging work from Dr. Amminger's group[1] on using omega-3 supplementation to prevent progression to psychosis, and I believe Dr. McGorry's group is currently working on a large trial using cognitive remediation techniques, an approach that also has support in the literature. In the animal literature, there is evidence that use of selective serotonin reuptake inhibitors (SSRIs) at a prepubertal stage can prevent the onset of behaviors relevant to psychosis in an at-risk mouse population, with an effect that persists long after the cessation of treatment.

Charles Schulz, MD: I think Patrick's points about the culture of treatment decisions will be an important part of this discussion. There is substantial anger about medications -- as we know.

Deciding Who to Treat, and With What

Dr. Strakowski: So how do we decide who to treat and with what? Pat, what kind of guidance can you provide clinicians?

Dr. McGorry: One of the most important areas in mental health research is exploring how to delay or prevent the onset of severe mental illnesses such as psychotic illness, especially schizophrenia. Twenty years ago, this possibility was out of reach. Now thanks to Australian-led research it is much closer. Yet despite the great potential for this emerging field to avert distress, disability, and death, it remains poorly understood within the community and the recent progress is often actively misrepresented in the media and public discourse. Such confusion and misrepresentation creates unnecessary public anxiety and risks weakening the imperative to provide safe forms of early intervention for those most in need. I am writing this with the goal of clarifying the issues, the latest evidence, and my views that are derived directly from the scientific evidence base and 20 years of clinical experience in this field.

Psychosis can be devastating for individuals and their families and weakens our society. Emerging in young people on the threshold of productive life, it poses a huge threat to health, career, personal fulfillment, and even survival. As a matter of equity, people who are experiencing psychosis or have a high risk of doing so should enjoy the same access to stigma-free quality care in a timely fashion just as is routinely the case with physical illnesses of comparable severity.

Just as with heart disease and cancer, every reasonable effort should be made to avert as much distress, discomfort, and long-term collateral damage from psychosis as is possible. What that means in practice is identifying the earliest opportunities for detection and intervention and the safest and most effective means of preventing and treating emerging psychosis. Our goal is to modify the impact and course of the illness; that is, to preempt the disabling aspects. Cure probably remains out of reach for most at this stage but substantially better recovery and long periods of freedom from illness are definitely attainable for the majority of people with psychosis.

Psychosis tends to first emerge in adolescence or early adulthood. Over the past 20 years, it has been demonstrated that early detection, optimum treatment, and support for recovery produce much better short- and long-term outcomes for young people experiencing their first episodes of psychosis. This evidence also shows that these better outcomes are achieved with lower costs so that precious resources are freed up and can be used to strengthen and expand mental health and social services for other groups of people including those with persistent illness, children, and the elderly.

Early detection and specialized care of young people with first episode psychosis and subsequently was the main international focus at first. Yet we have known for a long time that psychotic illness usually builds up over time and is preceded by "prodromal" features, which distress, disable, and attract concern and even stigma, yet do not yet manifest clear-cut psychotic features such as delusions and hallucinations. This held out the exciting possibility that we might be able to identify people who were "en route" to psychosis and not only provide care for their current problems, but also intervene to reduce the risk of progression to more severe and clear-cut psychosis. This challenge prompted a key breakthrough, developed originally by my colleague Professor Alison Yung and me in 1994, and elaborated since in many other international centers, which has enabled us to identify young people with high levels for risk of developing psychosis within the next year or so. This was the reliable definition of the "Ultra-High-Risk" mental state that predicted progression to psychosis surprisingly accurately. Young people in this ultra-high-risk group are already experiencing a range of mental health and social problems, are in need of care and actively seeking help. They can typically be expected to have between a 1 in 5 to a 1 in 2 chance of progressing to a first episode of psychosis within 12 months (that is between 200 and 400 times the rate within the general population). They also are at risk for other persistent mental disorders in addition to psychosis. In addition to the potential risk, which is significant, they are in immediate need of care for distress and impairment they are already experiencing. What that care should consist of is being actively studied and clinical guidelines have been carefully developed based on the evidence and experience accumulated to date.

The ultra-high-risk criteria have been studied further internationally and have been proposed as a new category in the next edition of the DSM-V manual, the US-based system of diagnosis in psychiatry. This proposal has been controversial, because of fears of extending antipsychotic medication more widely in the population and fears that

labeling people as being at risk (even if already experiencing mental ill-health) may be harmful. Both of these concerns are valid; however, both can and have been addressed in our work and systems of care in Melbourne.

One obvious benefit of the ability to engaging and monitoring young people with a high risk of developing such a serious illness is obviously in reducing treatment delays once the threshold to first episode of psychosis has been reached and thereby to facilitate better outcomes. But aiming higher, can being offered access to care as a member of the ultra-high-risk group benefit a young person by prompting care responses that delay or prevent the onset of a first episode of psychosis?

This important question has been a subject that I and other colleagues, notably Alison Yung, have been researching over the past 20 years. As a result of this and other research -- a total of 6 clinical trials now, we can now say that with appropriate intervention, it does appear to be possible to delay the onset of a first episode psychosis among members of the ultra-high-risk group. This finding, unimaginable 20 years ago, is highly encouraging because it gives grounds for optimism that further research may establish whether it is also possible to prevent the onset of a first episode of psychosis within this group. Several approaches to treatment that have been studied seem to be able to delay the progress to psychosis as well as alleviate the distressing and disabling symptoms that affect people at this stage of illness.

At the 7th International Early Psychosis Conference in Amsterdam, we launched the most recent version of the Australian Clinical Guidelines for Early Psychosis. These guidelines, which distill the very latest research evidence, specify that recommended interventions for this ultra-high-risk group are a combination of omega-3 fatty acids, cognitive behavioral therapy, and supportive counseling as well as, in some cases, medication for other diagnosed conditions that may be present (for example depression) as well as psycho-education for family members.

The guidelines explicitly state that antipsychotic medication should not be considered as a first-line treatment option for the ultra-high-risk group. Only in exceptional circumstances, where there is rapid worsening of psychotic symptoms combined with an elevated risk to the young person or others should consideration be given to the use of low-dose antipsychotic atypical medication. Even then, the use of antipsychotic medication would normally not be justified. The rationale for this is that safer treatment options should always be offered before those that carry increased adverse effects and risk. This is a fundamental principle in medical care: "first do no harm." Only if the initial safer option fails should progress to the next level occur according to a "staging model" that we have explicitly developed and described in recent publications. These guidelines restate and reinforce the earlier international guidelines produced by the IEPA in 2005 that my colleagues and I wrote in a collaborative fashion with other international experts. The evidence that has accumulated since strengthens the position taken in 2005 so there is no change in the position.

This last point about the use of antipsychotic medication within this group is very important because my stated position and those of my colleagues about this issue is occasionally misreported or misrepresented. There is a clear distinction to be made between research trials and clinical guidelines, a distinction that is sometimes not made clear. Our group in Melbourne has researched a number of potential interventions to reduce symptoms, disability, and risk in the ultra-high-risk group, including befriending, cognitive behavioral therapy, supportive case-management, family support, omega-3 fatty acids, lithium, antidepressants, and low doses of antipsychotic medication. All of this research has been approved by an independent ethics committee and all participants have of course provided fully informed consent to be involved. The results have demonstrated that not only supportive psychosocial care and case management, cognitive behavioral therapy, and omega 3 fatty acids, but also low-dose antipsychotic medication may be effective in delaying the onset of first-episode psychosis.

However, our clinical guidelines do not (and have never done so in the past) recommend the use of antipsychotic medication as the first line or standard treatment for this ultra-high-risk group. This is because other, safer interventions are equally effective in delaying the onset of psychosis and, despite the greatly elevated risk, it is equally true that at least two thirds of the ultra-high-risk group will not experience a first episode of psychosis, so

many could be receiving antipsychotic medications unnecessarily. The key issue is timing and careful consideration of benefits vs risks in consultation with the patient and their family within a shared decision-making framework. The most promising initial combination so far is omega-3 fatty acids combined with cognitive-behavioral case-management; safe and effective as first-line care. We therefore believe that further research would be required before it could be known whether and in what circumstances low-dose antipsychotic medication may have a role later in the sequence of treatment of the ultra-high-risk group. The current psychosis threshold may not be the only or best guide for this decision. Hence for some patients, in the era of short duration of untreated psychosis, even when they have crossed the threshold to fully-fledged psychosis, it may be that antipsychotic medications may able to be avoided or deferred if expert and comprehensive psychosocial care is available. This is something we are also researching.

In summary, we are trying to define the sequence of decision points for every patient based on the balance between benefit and risk, not only for the present day but also for the future. And not only for psychotic illness but for several other dimensions of mental ill-health. This is a mainstream evidence-based approach that is fully supported everywhere else in healthcare. We need to see it embedded in mental healthcare too.

Assessing Symptoms, SSRIs, and Clarifying a Misnomer

Dr. Tambyraja: I am particularly struck by [Dr. McGorry's] emphasis on the least harmful therapeutic measures that also have evidence to back them up, such as cognitive behavioral therapy and omega-3 supplementation, and that atypical drugs are essentially never the first-line treatment.

One question I had about that protocol was how to make the decisions about symptom severity and escalation of care. I assume that your group uses either the SIPS [Structured Interview for Prodromal Syndromes] or ARMS [Abnormal Involuntary Movement Scale] assessment instruments; are there specific scores or rates of decline on those instruments that trigger specific treatment decisions?

One of my first exposures to this field was Meyer's work on using SSRIs to prevent the onset of psychosis-like behaviors in rats. While the time-course makes that challenging to study in humans (in the animals it was given prepubertally to prevent effects post-pubertally, so several years in humans), I've always been curious about the use of SSRIs for the prodrome. I think Dr Cornblatt's work was an exciting hint in that regard, but I was also wondering your thoughts on the role of SSRIs as a "safer" choice than atypical drugs. Clearly, they might be used to treat comorbid depression, but any opinions on their use beyond that?

Dr. Strakowski: Rabindra raises 2 important questions: First, are there rating instruments that can be used to trigger when treatment moves from active observation to actual psychopharmacologic or cognitive intervention? Second, is there a role for SSRIs in that transition? Pat? Chuck?

Dr. McGorry: This raises the key question as to whether the intensification and persistence of positive psychotic symptoms should be the sole guide to the introduction of antipsychotic medications. With more research we may find that some people with "technical transitions" of 1 week or so of suprathreshold positive symptoms may not need antipsychotic meds, ie, the very short DUP/brief psychosis cases. We may also find that some people who do not and perhaps never do make a transition do benefit from antipsychotic meds. We are doing studies in this space from both sides.[2]

Regarding the SSRIs, while Barbara Cornblatt and Philip McGuire have made a circumstantial case for a role for SSRIs in reducing risk, their study designs were heavily biased in failing to control (as did NAPLS) drug therapies. In our studies so far, we have failed to find any effect either way (in triggering or in reducing transition risk). The issue is worthy of a randomized controlled trial in its own right because there are neuroprotective properties of SSRIs. One would need to measure risks too, especially suicidal ideation.

Alison Yung, MD: I am just joining in the debate now but have read the previous emails.

I think there are a few important issues [here]:

1. "Prodrome" is a misnomer and misleading because it implies inevitable progression to disorder. A key issue is that in all studies, including our long-term follow-up study that has 15-year follow-up on some individuals, the proportion of "at risk" individuals who develop a first episode of psychosis is less than 50%. In some services, it is as low as 10%-15%. Furthermore, the transition rate is decreasing, at least in our service.[3] So we must be mindful of (1) minimizing stigma; (2) using less toxic and more broad-spectrum interventions in the first instance -- this is consistent with the staging model[4,5];and (3) treating presenting problems, eg, depressed mood, accommodation difficulties, and so on.
2. There is a need to continue to evaluate factors that increase or indeed decrease risk.
3. We need to acknowledge that the definition of "transition to psychosis" is arbitrary and not necessarily indicative of the onset of schizophrenia. It may or may not be meaningful in terms of long term outcome, or structural or functional brain abnormalities.[6]

Identifying Risk Factors and Intervening Early

Dr. Strakowski: Thank you for your excellent comments. One interpretation that at least I take from this is rather than approaching these individuals as progressions to something else (schizophrenia, bipolar disorder), perhaps we should be thinking more generally about identifying and providing good care to young people who are at risk for mental illness because of: (1) genetics (family history), (2) trauma, (3) high stress (eg, loss of a parent), etc. Then instead of considering these 'prodromal cases' we consider them individuals who are already struggling with behavioral issues, which is why they come to attention, and who have risk factors for getting worse. Thoughts from the group?

Dr. Yung: I think that is a helpful way of thinking about things and certainly a useful guide for clinicians who have a distressed person in front of them. We do have to remember that the most likely outcome is that the patient will get better and the second most likely outcome is that apsychotic disorder will develop, so monitoring of mental state is important as well as treating current issues.

We also know that there are some risk factors that make development of psychosis more likely. One robust finding across a number of different sites and countries is poor functioning at baseline. Negative symptoms have also been found to be predictive in a number of studies (though not all), as has substance use. So patients with these features could be monitored more vigilantly or for longer perhaps.

Dr. Tambyraja: It may be somewhat off-topic, but this part of the discussion reminds me of the early intervention services offered to very young children (birth-age 5, typically). They can be receive services either if they're showing lagging development, or even simply based on risk factors such as teenaged mother, low birth weight, or other similar factors. There isn't a clear "diagnosis" in most of these cases, just an awareness from the pediatrician that the child's development is either at risk or is not proceeding apace. It's a pretty well-regarded program with good results.

I mention that because 1 key difference between those services and services for the ultra-high risk population is that nearly all young children make frequent visits to their pediatrician, whereas in many cases a teenager or young adult may not come to mental health services until more obvious problems are present. Provider awareness and the availability of the right psychotherapies can also be limiting factors. As Dr. Yung points out, a close look at the risk factors may help steer us towards which patients are at greatest risk, and thus most in need of help.

Dr. Strakowski: I think your comments are not off topic at all -- perhaps there is a suggestion here that we (psychiatry) need to work more closely with pediatricians, who do continue to see adolescents, to educate them

about the mental health risk factors, and collaborate more actively in decision making, to do exactly the same type of thing -- monitor young folks with risk factors.

Dr. Tambyraja: The answer on what services are provided by early intervention varies widely by state and county. In the urban area of Cincinnati, it provided for in-home visits by nurses to assess the home environment and provide counseling to the mother on child-rearing and playstyles that would foster development. It also provided access to social workers to help make sure the parents were aware of all the resources available to them (including programs at schools, libraries, etc). It assisted with access to specific therapy services such as occupational and speech therapy, depending on the child's specific needs. I believe there was also assistance with nutrition and dietary counseling, but I had less exposure to that side of it. Once in "the system" so to speak, it also became easier to access escalating services, depending on the situation.

[In terms of how] long to keep a patient on meds once they've been started for an acute symptomatic episode is a crucial one. I would guess that the predictors of doing well off meds would include engagement with psychotherapy and appropriate psychosocial support. I'd be very curious to hear your opinions on how long to treat with meds, assuming they were started for an acute episode of psychotic symptoms and were engaged in psychotherapy.

Dr. Schulz: Thanks to Rabindra for his thoughtful comments and his pediatrician views. Although we can speculate, of course, we would need some data on longer treatment with medications with specificity of what type. We have heard that not all "non-converters" do well over the next couple of years, so there may be need to understand their needs.

I would speculate that there are some people who seek our help who have a number of symptoms related to stress in their environment who can benefit from the combination of medication and therapy. In some cases as the problem solving of therapy helps restructure their lives, the need for medication may go down.

The Role of Primary Care

Dr. Tambyraja: Dr. Schulz and I had the opportunity to chat about some of the interesting questions this discussion has raised, and I'd like to bounce some of these off of this august group.

One thing we in the child psychiatry division have noticed is that given the chronic undersupply of child and adolescent psychiatrists in the United States, by the time patients arrive at our clinics, there is usually pretty significant dysfunction in their lives. Florid psychosis is not typical, but there usually has been a decline in function, and efforts to be seen by their pediatrician, perhaps a school counselor or a therapist along the way. In general, the more psychosocial risk factors present (low-income household, family chaos, etc), the longer it will take for them to finally be seen by a child psychiatrist, just due to some of the logistics involved. I worry that this will slow down their access to care, and may force us to start some of our interventions further down the algorithm.

Related to that, many times if patients have had positive symptoms, another provider such as a pediatrician or family practitioner will start them on low-dose antipsychotic drugs due to very high concern about the psychotic symptoms. In the short time I've been seeing ultra-high risk referrals, I've seen this twice, and in both cases the medicine has been well-tolerated and caused enough (or was closely related in time to) relief of symptoms that the patient strongly wished to keep taking it. I have to admit, I was reluctant to remove something that seemed to be bringing such relief, though I'd like to hear the group's thoughts on this, as I imagine it might be a common practice pattern in the United States.

Similarly, while I think we'd all agree that starting with psychotherapy models and close monitoring would be the ideal initial treatment most of the time, in many cases high-quality psychotherapy is not available, or has a significant wait time for entry. In those cases, are there interim measures we could suggest to pediatricians or family

practitioners who may be seeing these cases? Would most people feel comfortable recommending omega-3s as per Dr. Amminger's study, figuring it may help and couldn't hurt?

Putting It All Together

Dr. Strakowski: This discussion has been very helpful so far, and extensive. Could each of you summarize what you think are the key points for clinicians facing these at-risk kids?

Dr. Tambyraja: Thanks to everyone for a fascinating discussion; it's been a real treat to participate. In summing up our thoughts, I think Dr. Schulz and I agree on the following:

1. Accurate risk stratification is crucial, and a moving target at present. It's probably the most important research point moving forward, as the prognostic accuracy shifts the risk-benefit discussion for any treatment. Whether this stratification relies on clinical assessments, imaging, biomarkers, or (most likely) a combination of all 3 remains to be seen.
2. While we agree that nonpharmacologic treatments should be first-line, we also think that there is a role for medications, particularly for those patients for whom regular psychotherapy is logistically too difficult, or whose symptoms are more severe or disabling. We anticipate that the doses used would on average be lower than those used to treat schizophrenia, and may also include agents such as antidepressants or omega-3 supplements (based on Dr Amminger's work).
3. Building on the last point, the decision to start medication should be linked to criteria for stopping medication, such as improved function, frequency of monitoring, engagement in psychotherapy, and the enhancement of social/family supports.

Dr. Yung: [To summarize, here are] a few points:

1. "Prodrome" is a misnomer, as I noted before. I think it would be helpful to say "Treatment of potential prodrome" or even "Treatment of potential psychotic/schizophrenia prodrome."
2. I agree with [Dr. Tambyraja's] first point -- ongoing research is needed to identify risk factors, both for "transition" to psychosis and for long-term poor functional outcome. These 2 outcomes may or may not overlap.
3. Treatment should have 2 foci: one on the patient's current presenting problems. These might be depressed mood, family difficulties, or other social problems, in addition to the symptoms that define the person as "prodromal." Indeed the person may not identify their psychotic-like experiences as their main difficulty. The second focus should be monitoring of mental state for worsening signs of psychosis. Regarding the former, supportive therapy and practical help are usually effective and often psychotic-like symptoms resolve rapidly once various psychosocial stressors are managed. Regarding the latter: as noted below, supportive therapy, cognitive therapy, and maybe omega-3 fatty acids should be first-line approaches. (However, note that there is only 1 study of omega-3 -- we are trying to replicate this currently.) Antidepressants may be indicated if the patient is depressed, and these may or may not also be effective in reducing risk of transition (no randomized controlled trials to date, but some "ecological" evidence). Antipsychotic drugs should not be used unless there is evidence of rapid deterioration related to the psychotic-like symptoms.
4. I do not think antipsychotics are indicated solely because psychotherapy is logistically too difficult. I actually think that the nonspecific aspects of psychotherapy are highly beneficial (our UK colleagues would probably disagree with this). Together with practical help with finance, accommodation, school, or work issues, this treatment is likely to resolve many problems. Perhaps your patients are different from ours? We have a lot of people from indigent backgrounds (many with a history of childhood abuse) struggling with getting by each day. There are many problems with using antipsychotic drugs when not clearly indicated from a symptomatic point of view. Obviously, side effects are an issue, but also any improvement may be attributed to the antipsychotic drug when the person may have got better anyway.

5. Thus, I think Dr. Tambyraja's last point about criteria for stopping antipsychotic drugs is a good one. It would be good to research this idea!

By the way, we have written a book that might be of interest: *Treating Schizophrenia in the Prodromal Phase*.[7] It is a bit out of date now, but has detailed information about our different treatment modalities, service structure, and of course the conceptual underpinnings of these.

Dr. McGorry: I'm in total agreement with Alison. Regarding the timing and need for medication, perhaps an important distinction needs to be made between the patient who has presented with ultra-high-risk features and a need for care due to distress and significant functional impairment and then received the best psychosocial care with cognitive behavioral therapy, case management, perhaps omega-3s, treatment of depression (including, only if depression is moderate/severe a trial of antidepressants) and other diagnosable syndromes, yet failed to respond, and the patient who has a good response to these interventions at least at first. Persistence or worsening of subthreshold positive symptoms, especially if distressing or disruptive, tenacious negative symptoms and functional impairment, despite maximal treatment short of use of antipsychotics, even if formal transition as we define it has not yet occurred does justify a trial of antipsychotics in my opinion as a clinician.

Conversely, as our STAGES study contends,[2] some patients who have crossed the line to "first-episode psychosis," especially those with a rapid onset, short duration of untreated psychosis and diagnoses of brief psychosis, psychosis not otherwise specified, and schizophreniform disorder, who have not been exposed to maximal psychosocial interventions with or without use of SSRIs and omega-3 fatty acids, should potentially be considered for a trial of the latter before use of antipsychotic drugs, provided they meet key safety criteria (risk of suicide and aggression) and can give truly informed consent. Under these circumstances, this choice could be offered to a small minority of first-episode patients, but with a low threshold for dropout if there is no response within 6 weeks.

This approach does not tie the prescription of antipsychotic drugs quite so rigidly to the definition of transition based on positive symptoms alone but brings in the notion that stepwise care should be offered with interventions causing fewer adverse effects being offered first. It respects the Hippocratic maxim "first do no harm" and is sensitive to the benefit-to-risk ratio in early intervention terms as witnessed in cancer treatment and clinical staging generally.

Dr. Strakowski: Thanks to all of you for an interesting discussion. It seems clear that how we manage these at-risk patients is still a medical science in its infancy, but the very fact that we are finally attending to these young people, to think about early intervention and potential prevention of evolving severe mental disorders is a major advance in mental healthcare. Hopefully, our discussion will prompt others to enter this area of research and care development to propel advances as rapidly as we can, to the better health of our communities.

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