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Time needed to complete: 59m

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From Trial to Treatment: Translating Emerging Clinical Data into Meaningful Schizophrenia Clinical Care

Announcer:
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Dr. Correll:
Welcome to this program titled From Trial to Treatment: Translating Emerging Clinical Data into Meaningful Schizophrenic Clinical Care. My name is Christoph Correll, and I'll be covering with you today unmet needs in schizophrenia, goal setting, how it's relevant for functioning and life engagement, as well as the role and position of emerging treatments for schizophrenia, and how to put this together in a team approach.

As you know, schizophrenia is a heterogeneous concept, because it also has multiple domains, and not everyone has the same expression of symptoms in all of these domains. The classical ones are positive symptoms, negative symptoms, cognitive dysfunction, but patients have also motor symptoms, even independent of antipsychotic treatment, people, even before the antipsychotic era, had problems with tardive dyskinesia or with dyskinesia. There is cardiometabolic burden, even independent of schizophrenia treatments, because people with first episode illness have more insulin resistance than the healthy controls. There are affective symptoms. People with schizophrenia also have depression, anxiety, and can have suicidality. And the reward processing is a problem in people with schizophrenia, so addiction may be a self-medicating event. And all of these converge on problems with health and functioning.

Clinicians often focus on positive symptoms, maybe also negative symptoms, but it's symptom driven. This is the spearhead, and it's the tip of the iceberg that gets people into higher levels of care, into problems with society. Even negative and cognitive symptoms are often underappreciated by clinicians, not monitored and not addressed. But side effects are more seen by clinicians as a nuisance variable.

Patients, on the other hand, really put this very much upfront because they feel impaired functionally in their quality of life by side effects. So we need to balance efficacy and safety, not to lose patients, and retain their medication interest that they're taking it, there's something in there for them, and feeling altered in your body and your mind by medication, may be misinterpreting what's the illness and applying it, attributing it to the medication can be a problem. But we need to talk to patients about that. We need to understand their view and also appreciate that.

Patients report medication side effects a lot, report impairment in their daily life through it, almost 2/3-3/4 report the side effects, and 30% even report moderate to severe impairment in their daily life due to the results of medication side effects. Side effects can be disabling, and if they're not addressed, they can relate to distress, chronic health complications, and non-adherence, which then also creates a psychiatric problem.

So efficacy is the spearhead of what we are doing, but it's really only the beginning. Tolerability is relevant. It links via adherence to what we're really after, or should be after, at least what patients and families are after. That's the higher order outcomes beyond symptoms, subjective well-being, quality of life, and functional capacity. To achieve that, we need the bedrock of medication treatment, but we need

to flank that with psychoeducation and psychosocial therapies to enhance patients' capacity and have them reintegrate into society and their own lives, increase their self-esteem and their self-efficacy, ideally early in the illness, before they are really disconnected from educational and social environments, before their psychosocial fabric has been eroded by the illness and before patients also engage in self-stigma.

So what's the desirable aspect of an antipsychotic? Well, it should be efficacious, and ideally, not just for positive symptoms, but for negative, cognitive, mood symptoms, and ideally, even insight. We don't know where insight resides, and have really little treatments for it at the moment. It should be well tolerated, particularly not addressing adversely those five big side effect clusters of our current dopamine antagonist antipsychotics, EPS or tardive dyskinesia, prolactin elevation, both due to the blockade of postsynaptic dopamine receptors, weight gain, metabolic abnormalities, and problems with sleep. It should be easy to use to enhance adherence, ideally, once a day, maybe even a once-weekly antipsychotic would be nice. We have, hopefully, more options of long-acting injectables. There should be easy switch and titration schedules. We want to have a wide therapeutic index that people don't have with small increments of doses, big problems and side effects or even toxicity. We want the medications to be as uneffective as possible by hepatic and renal impairment. But the Holy Grail to the left is really social, vocational, and quality of life outcomes.

This cannot happen just with medications alone, as I mentioned before, we need to pair that with psychosocial treatments. But to do that, we need to set goals. We need to set goals with patients and identify what's important for them. Without that, we cannot do motivational interviewing, linking what we think is important for the patient to what's important to them.

What are SMART goals? Goals are SMART when they have five components, they should be specific, not nebulous. What is it that we're working on? They should be measurable? Is it something that we can then follow up on and see, have you achieved that? To what degree? They should be achievable. Patients with schizophrenia have enough reason to be frustrated and not achieve what they achieved before. So small steps, steps that are doable. But also the goals should be relevant. If the outcome is only relevant for us and not the patient, we've lost them. And they should be time bound; that's part of the achievability. And having a horizon of several years doesn't work; we need small steps with immediate or close to achieve rewards.

But to set these goals, we need to know where the patients are and also what they want. What's relevant for them? We may not get that in the first encounter, but we should strive to get to know the patient better in order to then understand what makes them tick, what makes them want something? Is it in the social and family realm? Is it in the physical health domain? What about living arrangements? Or what about occupational and financial desires? Again, they should be doable, these goals; they should be achievable, and we may have to sequence them easier things first, building a block from which upon we then can start endeavor these other goals.

But this is not done in isolation, neither for the patient nor for us. During the planning, we should set priorities, appraise the strengths. We're often so deficit-based in psychiatry and in medicine. Select strengths, work with them, build upon them. We need to select appropriate interventions, but also determine resources, human resources, but maybe also technological resources or online resources. And we need to work together. We need to clarify choices, identify environmental options, personal values, and personal interests.

In order to help patients achieve the goals they want to achieve, and have good patient-centric decisions and discussions about treatment goals and options, we should assess what's relevant to the patient, inquire about their goals, acknowledge that relapses or setbacks may occur, but that we're there for them. Emphasize the link between consistent medication treatment and better functioning. And convey that if bothersome side effects occur, we can do something about it. So it's important that this is a package, and the patient feels that supported by us.

Shared decision-making should be informed shared decision-making. So the clinician provides knowledge about the condition, inquires about patient preferences, shares insight about treatment options. But the patient also shares their experience, their expert experience, their values, what they prefer, voices concerns that we need to address, and asks questions to the provider, as we should ask questions to the patient. So we share this space of identifying what the illness is, where it's going, how it has affected the patient, and what we can do to help the patient navigate the illness better and hopefully identify goals and steps towards those goals that hopefully also involve the treatments that we believe, based on data and experience, can help the patient best to get there.

Now, novel agents are relevant, because not everybody is currently helped well enough with the current treatment paradigm. As a matter of fact, chronic patients, about 1 in 2 and 3, have a response. Half have remission, that's at least 6 months of no more than mild symptoms, positive and negative, but only 16% or less, 13% actually, have recovery. That's symptom stability and functionality. So it goes from 2/3 to 1/2 to 1 out of 7. In first episode patients, it goes from 80% that have a good response reduction in symptoms to a little more than 1/2, maybe 60% have remission, but only 20%, 1 out of 5, is in recovery. And that's partly due to ongoing positive, negative, and cognitive symptoms that then interfere with goal attainment.

So despite the foundational effects of dopamine antagonists and partial agonists, issues remain that there are residual positive,

negative, and cognitive symptoms. There's treatment resistance. We now know that about 20% of all schizophrenia patients are treatment resistant from the first episode. Treatment resistant from the first episode, that then doubles to 40% as patients relapse. Identifying them early and maybe having different treatments that can counter the treatment resistance by treating the presynaptic dopamine that is too high and not only cover the postsynaptic downstream effects, might actually be helpful. So efficacious, safe, and novel mechanisms of action are desired. These agents are desired. They may be used as a switch agent in augmentation or an alternative option to either minimize adverse effects due to the current treatment paradigm of postsynaptic dopamine blockade, they may expand efficacy for unaddressed domains like negative and cognitive symptoms, achieve efficacy in partial non-responders or even in refractory illness, and they may augment efficacy of current agents and partial responders when given as augmentation agents. And finally, the hope is that either in monotherapy or in combination, they may improve subjective well-being, quality of life, and functionality. Obviously, this all needs to be studied when these medications become available. And you and I, we will need to also try it out with our patients.

So in conclusion, to treat people living with schizophrenia effectively, we should not only focus on positive symptoms, but go beyond that. That includes negative and positive as well as negative and cognitive symptoms, as well as functionality. Substance abuse as a comorbidity, affective symptoms, but also physical health conditions that may be due to ongoing illness and maybe even our treatments. The concept of life engagement includes psychiatric symptom stability, functional recovery, but also fostering a sense of agency, self-efficiency, and meaning through connectedness to oneself, one's brain, people around one, and also one's goals. Collaborative care and motivational interviewing can strengthen the treatment alliance that has been shown to be very relevant in people with schizophrenia and other mental disorders, identify their goals, pursue them, and improve outcomes. Hopefully new mechanism of action medications can be part of the solution, but stratified care and targeted pharmacological or psychosocial treatments may need to be developed. May some of patients be more likely to respond to a new mechanism of action or a combination of the current mechanism and a combination with a new mechanism? We will have to find that out and we need to move beyond just the only availability of one treatment mechanism right now, which is receptor blockade or partial agonism Postsynaptically. And that's the first step, which will be followed by real-world impact testing of these novel agents that hopefully can improve overall outcomes.

So thank you very much for your attention, and I hope this was helpful.

Announcer:
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