SPEAKER NOTES

A Different View of Antipsychotic Medications

Summarized by Thomas T. Thomas

At the Wednesday informational meeting on May 28, we heard from **Demian Rose, MD, PhD,** Professor of Psychiatry, Weill Institute for Neurosciences, UCSF School of Medicine. He has been involved with the Psychiatry Department's Path Program for Early Psychosis (https://pathprogram.ucsf.edu), a coordinated specialty care clinic and research center focused on early recognition and treatment of psychosis. He has spoken about his work at NAMI conferences and is a leader in the field. At our meeting, he discussed new ways to conceptualize the use of medications.

The Path Program is part of a state-funded initiative with the goal of helping patients live well across the lifespan of their illness. Early intervention applies to someone who meets the threshold criteria for psychosis. Generally, this occurs in the late teen years to early twenties, but in a few instances may occur in the early teens or in the late twenties and early thirties.

In introducing his remarks, Dr. Rose stressed that he is not anti-medication but that he considers the way antipsychotic medications are sold to be problematic. Almost all medications sold as antipsychotics block dopamine neurotransmission in one way or another.[1] "Antipsychotic" is an FDA classification based on intended use, which is generally recognized as reducing schizophrenic symptoms. "But you have to think about what a drug does when you take it," he said.

Dr. Rose asked the audience what they think dopamine does and got answers like "motivation" and "joy."

The brain is a complicated system, he said, and dopamine is involved in activities ranging from motor function to experiencing pleasure, or *hedonia*. In the case of psychosis, dopamine is related to what he called "perceptual salience." Salience is the brain paying attention to a person's surroundings and what matters. It focuses attention on intrusive and fixating qualities of stimuli. It assigns reward to certain stimuli based on a person's learning history—that is, the relationship weight you give to an idea, object, person.

Thoughts have a perceptual quality, he said, and attention is largely unconsciously generated.

Hyper salience is a quality of people who are vigilant. They note every new person in their visual field as possibly being important. If their perceptual field is too wide, they assume there is meaning in any coincidence between two people, objects, or ideas. And when salience is blocked, they feel the world is dull, gray, distant, far away, uninteresting—containing little of creative interest or relevance. Hyper salience, he said, is associated with stress.

[1] The exception, he noted, is Cobenfy, which contains xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist. By targeting the M1 and M4 muscarinic receptors, they may indirectly impact dopamine transmission.

This all leads to thinking about how medications might be helpful or harmful.

A fixation occurs when topics and themes invite long periods of analysis and a large emotional response. The person may be replaying the memory of some stimulus, interrogating it for details and motives that might help to explain it—but that's not the way memory works, because each time a memory is replayed it tends to change. The person will be trying to make sense of seemingly related people, objects, or ideas to simplify their understanding and increase their certainty. When a fixation is blocked, the person may feel out of touch with the world. He or she may be craving for meaning in the given set of situations.

Visual and auditory hallucinations, Dr. Rose noted, depend on the person's belief in their source: whether internally generated as a salient thought or externally generated as a physical stimulus.

Blocking dopamine changes a person's experience. Whether you have schizophrenia or not, taking dopamine will make you feel more hesitant than decisive, have fewer creative ideas, and feel indifferent rather than passionate. You will feel less emotional intensity and experience impeded flow of thoughts. With schizophrenia, the dopamine-blocked state inhibits hyper-salient perceptions, over-valued ideas, hyper-intensive thoughts and sensations, and hyper-associated thinking. In this way, the antipsychotic medications can help with agitation, irritability, and dysphoria.

Studies of pharmacology and clinical response to dopamine blockers indicate that, of the people with a diagnosis of schizophrenia or schizoaffective disorder, the range of improvement in symptoms varies widely. About 20 percent of patients experience no appreciable benefit or only experience harm. And about 40 percent experience a moderate to large benefit. This leave, Dr. Rose said, the "messy middle" of the 40 percent who experience small to moderate benefits, which must be weighed against short- and long-term harms.

The harms from these dopamine blockers may include weight gain, movement disorders, and reduced brain states. "You shouldn't give medications all of the credit and none of the blame," he said.

With early intervention, there is the thought that if you don't start medication immediately, the symptoms will get worse. But this is not true, he said. If there is a large benefit, then medication is worth taking. But if after a number of trials, the patient experiences no benefit, it's time to try something else.

"Something else," in Dr. Rose's terms, would include long-term psychotherapy with an individual therapist; family groups—involving the patient with his or her significant relationships—to focus on problem solving, especially in terms of disrupted development; and supportive employment.

As to trying different medications and dosages, he noted that dopamine blockers and most other medications do not bind to brain receptors in a linear fashion. That is, the higher the dosage, the lower the additional effect. And at the pill sizes that most drug companies make, the smallest dosage usually has the most effect. A double dose is not necessarily doubly effective. So, Dr. Rose's recommendation is to always start low, and you may not need to increase the dosage.

And going off a medication is also not linear. Reducing dosage as if the effect were linear increases the withdrawal symptoms. The proper way to reduce medication is to drop the dosage fast at the start and then go slowly, as the body needs time to readjust.

Dr. Rose's "take homes" from his presentation include:

- The medications the FDA approves for schizophrenia mostly act by blocking the neurotransmitter dopamine.
- Dopamine blockage has predictable effects on cognition and perception.
- These effects may be helpful for some people but harmful for others.
- On average, most people get small to moderate benefits, while some people get no benefits at all.
- Regardless of the medication's benefit, doses of double or triple the average do not seem to have appreciable effect on the outcome.
- Symptoms may start to come back if you have been following the medication regimen for two to three years.
- Your body will get used to any medication you have been taking for years; so, you can't stop taking it quickly.

"Generally," he said, "people don't like taking medication. People don't like the idea that there's something wrong with their body. And people on many other medications, like for blood pressure or cholesterol, have issues with compliance, too."