



Photo by: Judy Siegel-Itzkovich

Glutamate: The next psychiatric revolution

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Dr. tells *Post* how new medications will change the lives of patients with schizophrenia, other conditions.

The great psychoanalyst Sigmund Freud thought that his favorite technique could treat every mental disorder. He also often blamed parents – especially mothers – for the psychiatric problems of patients. He was exaggerated, but psychoanalysis can relieve neurosis, personality disorders and other mental problems.

In recent decades, psychiatry has swung to the opposite end of the spectrum – regarding mental illness as a biological disorder involving imbalance of chemical brain messengers called neurotransmitters that can be relieved – even if not perfectly without side effects – by medications.

“You don’t have to throw the baby out with the bath water,” says Prof. Uriel Heresco-Levy, chief of psychiatry at Jerusalem’s psychogeriatric Herzog Hospital.

“There are mental problems that can benefit from psychotherapy, but there certainly are patients with mental illness such as schizophrenia and depression who can benefit from medications, and a new era to treat such psychiatric disorders with drugs is ahead,” he told *The Jerusalem Post* in a recent interview in his office. Even Parkinson’s disease, which is a neurological disorder, seems to involve psychiatric symptoms that can be relieved with “modulators” of neurotransmitters.

Clinical depression is clearly a problem of the connectiveness of the synapses [gaps between neurons] in the brain. and neurotransmitters apparently are involved in schizophrenia ,” said the Romanian- born psychiatrist, who is director of Herzog’s schizophrenia research program. Heresco-Levy, who also teaches at the Hebrew University-Hadassah Medical School, has spent two decades doing pioneering investigations of the neurotransmitters glutamate, glycine and D-serine.

Taken from the Greek words for “split” and “mind,” schizophrenia has nothing to do with to multiple personality disorder in which a patient adopts different personas.

Schizophrenia is a psychosis with disorganized thinking and incoherent speech, abnormal perception or expression of reality, auditory hallucinations, paranoid or bizarre delusions and major social and occupational dysfunction.

Someday, said Heresco-Levy, it may become routine for schoolchildren with serious behavioral problems to be screened for early symptoms and markers of schizophrenia.

Those found at risk may be given naturally occurring amino acids to delay or even prevent the onset of this currently incurable psychiatric disorder.

In schizophrenia, patients have what are called “positive” and “negative” symptoms can be alleviated with medications. “Positive symptoms are not beneficial, despite the term,” said Heresco-Levy, but include phenomena whose presence is abnormal such as hallucinations and thought disorganization, while negative ones refer to deficits, or the lack of normal behaviors.

There are also cognitive symptoms such as memory problems and learning difficulties. Drugs that block the receptors of the neurotransmitter known as glutamate mimic the positive and negative symptoms and cognitive problems involved in schizophrenia. The positive symptoms include delusions and hallucinations,

while the negative ones include apathy, reduced emotion and lack of initiative.

Anywhere from 0.4 percent to 1% of the population are affected by schizophrenia, and it equally hits men and women of all races and ethnic backgrounds. The cause of great suffering to patients and their families, it is regarded as the most disabling mental disorder.

Most schizophrenia patients have a low socioeconomic status because the disease brings about drastic impairment of social and occupational skills.

“When a child is diagnosed with schizophrenia, his parents feel guilty. Today we speak about a biological disease involving brain development. Expressed emotions such as criticism, rejection and emotional overinvolvement don't cause the disease, but once it occurs, such factors can make it more serious,” added Heresco-Levy, who earned his MD at Tel Aviv University's Sackler Medical Faculty and specialized in psychiatry at Herzog.

In the early 1950s, chlorpromazine (Thorazine) – originally an anti-nausea treatment that also alleviated psychotic symptoms – was the first anti-psychotic drug, but it was not specifically meant for schizophrenia.

Working as an “antagonist” to dopamine, it blocks dopamine receptors on the ends of nerve cells and was found to improve “positive” symptoms significantly but not the “negative” and cognitive ones. An agonist is a chemical that binds to some receptor of a cell and triggers a response by that cell. Agonists often mimic the action of a naturally occurring substance. While an agonist causes an action, an antagonist blocks the action of the agonist. Schizophrenics have average life expectancies that are 12 to 15 years less than others because of higher suicide rates and physical problems for which they don't seek medical help.

The earlier generation of anti-psychotic drugs, which were dopamine suppressors, came with Parkinson disease-like side effects. Many institutionalized patients, recalled Heresco-Levy, were affected by muscular stiffness, tremor and involuntary movements.

“Today, we are far from having an ideal treatment, which causes frustration among psychiatrists. That is a major reason why I like to combine research and clinical work.”

Among the many types of neurotransmitters that make brain activity possible, amino acids such as glutamate, glycine and D-serine were chosen by Heresco-Levy for his laboratory and clinical studies.

Sixty percent of neurons use glutamate as their main neurotransmitter.

Glycine, the simplest type of amino acids found in the protein of all plants and animals, is released into the synapse. Glutamate, glycine and D-serine affect the function of the N-methyl-d-aspartate (NMDA) receptor. This type of glutamatergic receptor is found to be abnormally low in number in the brains of autopsied schizophrenic patients. Furthermore, it plays a crucial role in brain development and cognition.

IN THE early 1990s, Heresco-Levy was doing a research fellowship at Yeshiva University's Einstein School of Medicine in New York with Prof. Daniel Javitt, a world pioneer in glutamate research. “While studying antagonists of NMDA-type glutamate receptors, we reasoned that if NMDA antagonists cause schizophrenia-like symptoms, enhancing the functions of such receptors might help against schizophrenia.”

He has since used a combination of regular antipsychotic drugs combined with glycine and D-serine, which are natural amino acids in the brain and stimulate NMDA function. “The results were interesting; there were fewer negative symptoms.”

They worked on the drug phencyclidine, a “street drug” with hallucinogenic effects that is also known as PCP or “angel dust.” PCP works mostly as an NMDA receptor antagonist, which blocks the activity of the NMDA receptor and, like most ant glutamatergic hallucinogens, is significantly more dangerous than other categories of hallucinogens.

Glutamatergic drugs have been found to work in some but not in all studies. These compounds seemed to work better with treatment-resistant schizophrenia patients, and the pharmaceutical industry is now developing synthetic drugs that mimic glycine and D-serine actions, but no glutamatergic drugs are yet being marketed.”

He has no doubt that the next generation of schizophrenia treatments will be drugs involving the action of glutamate in which it functions as a transmitter. Heresco-Levy is also convinced that such drugs can also help patients with chronic depression and the motor and mental symptoms in Parkinson's disease, which causes not only shaking and difficulty walking but also a persistent feeling of sadness and loss of interest.

“For years, there were not many new things in psychopharmacology and the treatment of neuropsychiatric diseases,” said Heresco-Levy.

“New drugs that were introduced during the last 20 or 30 years were ‘me-too’ medications based on the same mechanism of monoamines, adrenalin, dopamine, acetylcholine and serotonin.

However, research he and others have done on glutamate offers promising understanding of what causes the diseases and new treatments.

“It’s surprising that this field hadn’t been researched for so long.

It is very important but complicated, as it involves different receptors systems in the brain,” the Herzog psychiatrist said.

“A large amount of glutamate is toxic in the brain and elsewhere in the body, so there was reluctance to deal with it. We were among the first researchers in the world into NMDA receptors.” Today, Javitt comes to Israel from time to time and has two or three other research groups at Harvard and Yale.

Heresco-Levy conducts research on glutamatergic medications alone at Herzog.

“We have shown that schizophrenic patients who get NMDA agonists, they show an improvement in their negative symptoms, such as apathy, difficulty in personal relations and a lack of pleasure,” the Herzog psychiatrist added.

His most recent research, involving small patient studies, were published in Movement Disorders and the International Journal of Neuropsychopharmacology.

Although they involved only a few dozen patients each, they were clear cut and convincing.

Today, the Roche pharmaceutical company is conducting phase III trials on glycine reuptake inhibitor for schizophrenic patients. “The drug companies have no interest in natural compounds because of patent difficulties, so they prefer new synthetic compounds. This is good because we expect this approach will bring a revolution in psychiatry, the first since the emergence of dopamine and serotonin drugs. Our schizophrenia research on NMDA agonists affects not only negative symptoms of the disease but also motor drug induced symptoms,” Heresco-Levy said.

AS FOR depression, this problem is major, as 30% or more of sufferers don’t react well to anti-depression drugs. There is a critical time lag, he said. “It takes weeks from the moment they are first taken until they have an effect. This lag is critical, because they could be suicidal without benefit from drugs. There is a new hypothesis that the problem is due to a decline in the plasticity of a synapse’s connectiveness. We believe that NMDA antagonists can help.”

At Yale, much attention was given to studies in which ketamine – used as an NMDA receptor antagonist – was given intravenously to the clinically depressed. This drug is used in both human and veterinary medicine to induce and maintain general anesthesia, usually together with a sedative. It is widely used including for treating pain, high blood pressure and for asthma symptoms.

“The researchers found that depressive symptoms declined significantly in a few hours, and the beneficial effects remained for up to two weeks after it was administered one time,” he continued.

“The problem is that it has side effects, and intravenously, it is not pleasant. We thought that if NMDA antagonism is a mechanism against depression, if we delivered it to other locations of the receptors, maybe we can make it effective.”

Heresco-Levy noted that there is an existing drug used as an antibiotic for tuberculosis that was approved by the US Food and Drug Administration for 40 years. Called cycloserine (its commercial name is Seromycin), it was found serendipitously to be a partial agonist for NMDA. “We took patients with treatment-resistant depression and added Seromycin – and they were much improved. We showed that the mechanism against depression is new.”

In the coming decade or two, Heresco-Levy concludes, the revolution of glutaminergic drugs will be upon us. “Major companies work in this field today. There will be fewer patients who have to be confined to psychiatric hospitals. Today, most of the inpatients have schizophrenia resistant to drugs. If we can find something better for them, it will change the whole mental health system. We are still far from it now, but when it is shown effective and is widely accepted, they will be able to live in the community and be employed in protected work. Patients with schizophrenia and other disorders will have much less stigma. Most treatment will be in the community.’