CureSZ Research | Recovery | Hope

CURESZ FOUNDATION Newsletter

ISSUE 31
SUMMER 2025

Comprehensive Understanding via Research and Education into SchiZophrenia

The US Clozapine Package Insert Needs Major Changes

by **Jose de Leon,** Professor of Psychiatry, University of Kentucky, Lexington, KY

The author acknowledges Lorraine Maw, M.A., from the University of Kentucky Mental Health Research Center at Eastern State Hospital, who helped in editing the article.

Clozapine's Package Insert

Clozapine is an antipsychotic approved for two conditions: treatment-resistant schizophrenia (TRS) and reducing suicidal behavior in schizophrenia. No other antipsychotics are approved treatments for these conditions. In the United States, the Food and Drug Administration (FDA) approves drugs. In 1989, the FDA approved clozapine for TRS using a study headed by Dr. John Kane. In 2003, the FDA added the other condition, suicidal behavior. To gain approval, the marketing pharmaceutical company must develop a complex bureaucratic document called a package insert, or drug label. In the FDA's view, package inserts educate prescribers in a drug's pharmacology. In reality, package inserts are seriously hampered by extreme length and complexity. However, all US prescribers know that lawyers can use package inserts against them in court. Package inserts use boxed warnings (previously called black boxes) for potentially lethal adverse drug reactions (ADRs).

Clozapine's History

In 1975, after clozapine was marketed in Europe, the Finnish drug agency reported eight deaths associated with agranulocytosis in clozapine-treated patients, leading to the cessation of US studies. Agranulocytosis refers to a significant decrease in some white blood cells (WBCs) called neutrophils, needed to fight infections. FDA approval required a complex hematological monitoring system, the use of a centralized database for WBC counts, and a boxed warning for agranulocytosis.

Clozapine Was Not Studied as Current Drugs are Studied

The introduction of new drugs in the US now requires more sophisticated studies than those completed for clozapine. They include studies on:

1) basic pharmacology, and
2) ADRs.

Furthermore, after marketing, the FDA is required to monitor potentially lethal ADRs in a process called pharmacovigilance and modify the boxed warnings accordingly. Pharmacovigilance varies in other national drug agencies, based on economic resources. ADR reports from all drug agencies are sent to the international database, called VigiBase, which is managed by the World Health Organization (WHO).

My History and Clozapine

In 1987, after being trained in medicine and psychiatry in Spain, I trained in Philadelphia as a clinical scientist in psychiatry. My Spanish wife and I had no choice but to stay in the US, as the Spanish university did not hire me to teach. Our first two children were born in Philadelphia during our first nine years (1987-1995) in the US. I conducted research in state hospitals, including supervising a clozapine study for five years for my boss, Dr. George Simpson, who published the first clozapine study in the US. In 1996, we moved to Lexington, Kentucky, where our youngest daughter was born. First, I managed a 30-bed unit for treatment-refractory patients at Eastern State Hospital. I converted it to a research unit by measuring blood levels and adding a laboratory to research genes that control the medication metabolism process. Second, over the last 20 years, I worked as a consultant for the state of Kentucky:

1) helping with the most difficult cases at the state mental health facilities
2) reviewing patient deaths and
3) developing pharmacological guidelines.

Prior Major Clozapine Articles

In 2019, I wrote an editorial on clozapine package inserts proposing that:

1) patients of Asian ancestry only need half the US-recommended dosage
2) slower personalized titrations prevent clozapine-induced myocarditis (an inflammation of the heart)
3) pneumonia is the most frequent cause of death in clozapine-treated patients.

During severe infections, including pneumonia, the body's ability to metabolize clozapine is impaired, so if clozapine dosing is not stopped or decreased, the patient develops a very dangerous combination of pneumonia and clozapine intoxication. After 9 rejections of my editorial, the 10th version[1] was published in Schizophrenia Research (a journal founded by Drs. Nasrallah and DeLisi) and included Dr. Kane as an author. The gracious support of Dr. Kane had little impact on the FDA and clozapine experts worldwide.

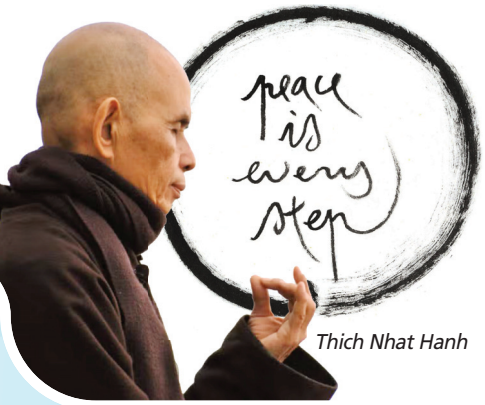
In VigiBase, until 2019, among worldwide clozapine-treated patients, there were:

1) 34,491 reports of agranulocytosis with 550 deaths
2) 6,983 reports of pneumonia with 2,077 deaths.

In February 2020, the editor of the journal that published our article sent it to a psychiatric colleague working at the FDA. The FDA psychiatrist informed me that the article was forwarded to the clozapine team, but I should not expect to hear back from them. I was relieved; the COVID-19 pandemic was starting and it could cause COVID-19 pneumonia in clozapine-treated patients. I thought the FDA might choose to save thousands of lives worldwide by modifying the clozapine package insert. I was wrong; nothing happened.

continues on page 4

WhatSZ IN THIS EDITION



Thich Nhat Hanh

SCHIZOPHRENIA SURVIVORS

Rose McDuff, PsyD *(Pseudonym)*

From Psychosis to Psychologist

Growing up, Rose had a winsome personality and was a highly capable student. Pursuing a decades-long interest in psychology, she entered a doctoral program in psychology in her early 30s, performing well for four years.

In 2015, her life went off course. She developed visions and experienced what she termed "heightened spirituality." She went on long walks, saw people meditating in the sky, and believed she was performing shamanic ceremonies. Her studying was hampered by distraction from thoughts of telepathic communications with others. Her doctoral program required trainees to undergo therapy. In one session, as she described her experiences, she thought to herself, "This sounds like schizophrenia," but quickly reassured herself that that could not be true. Her therapist did not express anything out loud about her possibly having schizophrenia.

Difficulties studying made Rose decide to take a leave of absence from school, returning to her home state. Using a previously earned masters degree in Community Counseling, she found employment as a therapist in a community mental health agency. Increasing paranoia made it difficult to work and get along with her coworkers. Conflict with her supervisor over her performance led to loss of that job. Soon, without income, she depleted all her savings, and was paying for her studio apartment and other needs on credit.

In 2017, for no apparent reason, Rose began to believe the FBI was monitoring her. She sent a series of accusatory texts to her sisters, her doctoral program faculty, and old friends she thought were colluding with the FBI. In her vision, a Mexican cartel murdered therapists where she last worked. Distressed by this, she spent the next day on a bench mourning people she believed were killed.

After receiving some of Rose's texts and concerned messages from her friends, her older sister sprang into action. Her sister investigated state policy on emergency mental health interventions and found a "Persistent and Acutely Disabled" (PAD) category that allowed involuntary hospitalization with a psychiatrist's and judge's approval. PAD meant that a person's health was deteriorating and would likely worsen without mandatory treatment.

One of Rose's friends helped Rose's sister complete the necessary paperwork, and police arrived to take her to a mental health evaluation. Rose was hospitalized for two weeks, and proceedings began for court-ordered treatment. Despite being delusional, Rose was able to learn what arguments could circumvent involuntary treatment and convinced a judge's representative that she was mentally stable and did not need medication, leading to her release. On arriving home to her apartment, she learned she was about to be evicted for nonpayment of rent.

For the next two months, Rose intensely believed she was fighting for justice from the FBI and that the secret service was protecting her. Her sister and mother again sought and obtained involuntary hospitalization for her under the PAD protocol. However, the prosecuting attorney was on vacation, and her hearing was deferred. Rose was released to await a scheduled court date.

Home again and annoyed by her family and friends sending police to check on her, she wandered around their neighborhoods pounding on doors to inform people how it felt, until police were called. She resisted arrest and was jailed for one night. Psychiatric evaluation at the jail resulted in her placement on mental health watch.

Upon Rose's release from jail, her sister secured her transfer right away to a psychiatric institution, to await her pending court case. Based on testimony of the arresting police officer and concerned family and friends, Rose received court-ordered treatment requiring her to take a small antipsychotic medication dose. Feeling persecuted, she refused to speak to her psychiatric nurse practitioner, instead working with a lawyer to gain hospital release. Eventually she was sent to residential care for recovery, and when released, she was court ordered to take a large paliperidone injection. The hospital discharge paperwork she received documented her diagnosis as "paranoid schizophrenia." She cringed upon reading it.

Soon Rose began to realize that she had been delusional and that her roommates could not possibly be a part of the secret service. The medication allowed her mind to clear, and her delusional belief system collapsed. She began restoring relationships and rebuilding her career. She started by calling her mother and tearfully asking for help.

The recovery process was slow and painful. It involved apologizing, securing employment, and undergoing psychiatric treatment with medications and psychotherapy. In an emotional phone call to her university's dean, Rose explained that she had been ill with schizophrenia but was recovering. He expressed relief that there was an explanation behind her erratic email messages and said he believed that just like Elyn Saks, Rose could also succeed.

Rose returned to school in January 2019 to resume work on her dissertation. Concurrently she worked full-time first as a peer support specialist and then as a mental health clinician. She underwent weekly individual therapy and exercised regularly. She attended support groups and made friends with peers who appreciated the stigma of mental illness and the accompanying shame. Despite this progress, she still couldn't fathom having a worthwhile life given her diagnosis of schizophrenia. She felt a lot of despair about her life prospects.

continues on next page

Encouraged by her dissertation chair and university advisor, Rose applied for internships to complete her doctorate. Having to disclose her psychiatric and legal history was stressful, and she received assistance in crafting skillful yet honest wording of her experiences. Happily, she was offered multiple interviews nationwide. She traveled to interviews across the country and matched with an APA-accredited internship in the Midwest which she began in 2020.

Wondering whether medication was still necessary, Rose worked with her prescribers to slowly discontinue it. This led to another psychotic episode, in August 2021, precipitating a month-long hospitalization followed by a one-month partial hospitalization program. She was stabilized on monthly paliperidone injections, driving a 90-minute round trip for each. She began to grapple with the realization that medication would be a life-long and sometimes inconvenient necessity. An understanding site supervisor supported her recovery and her family looked after her. Rose proudly completed her doctoral degree in September 2021. She attended the graduation ceremony and celebrated with her family via Zoom.

In November 2021, Rose began a postdoctoral fellowship via telehealth at a private practice clinic. She struggled with recurring feelings of despair and shame fueled by the diagnosis she carried and the painful memories of being ill, especially the delusions. Living alone with few interactions other than with her parents deepened her negative emotional state.

In the summer of 2022, she moved back to her home state to be near friends and family. These renewed relationships helped fend off her despair and enabled her to continue to move forward with her career. She used her own training to combat her feelings of worthlessness and followed a regular schedule that got her out of bed when she didn't feel like it.

Rose reflects that her treatment and subsequent recovery required not only skillful medication management, but also social support and connection with a sense of purpose and a renewed understanding of her spirituality. She listened to hours of the Zen master Thich Nhat Hanh on communicating effectively and learning to love oneself and others. She practiced mindfulness and meditated. The combined strength she gained from all of these pursuits enabled her to overcome the limitations of her psychiatric history and realize her dreams.

Rose applied for a psychologist license. She agonized over what to reveal about her psychiatric and legal history, spending months gathering the required documentation and carefully wording her history. She hired a lawyer, and had to present her case at numerous board meetings and complete a fit-for-duty evaluation. The licensure board offered her a consent agreement conferring the psychologist license under conditions of her compliance with its required provisions. She agreed and was awarded her license in March 2024.

Rose is currently supervised as a new psychologist until June 2025, when she can practice independently. She is grateful to her friends, family, university, internship supervisors, and state licensing agency for their forward thinking about what is possible despite a history of schizophrenia. Most importantly, she rejoices in her ability to care for herself and help others. Her psychiatric illness did not, as she feared, destroy her life and career, but these experiences have deepened her capacity to love and help others.

"(Rose) rejoices in her ability to care for herself. These experiences have (also) deepened her capacity to love and help others."

COMMENTARY

The account of Rose's story in this issue of the Newsletter is remarkable for her victorious outcome owing largely to her courage and tenacity. Secondarily, her account is also quite remarkable for the unusual response from the administrators of her doctoral program who actively supported her and did not reject her from continuing in their program. Other people in a similar position have not been so fortunate, even being barred only for having a history of mental illness from completing their professional education.[1] This blowback to the unfortunate occurrence of such affliction adds unnecessary pain to the immense suffering caused by the psychiatric illness itself.

The stigma of mental illness runs deep in our society. It permeates even where one might least expect it: in the medical and mental health professions, which should be expected to do better, but have demonstrated that even they can be among the worst offenders.[2] People who recover from serious mental illness should be celebrated, not rejected based on their psychiatric history. Such barriers to reconstitution of their lives can not only threaten their hard-won victory over the illness but may also prevent them from realizing potentially far-reaching and well-deserved psychosocial gains after their recovery.

Fortunately for Rose, the pioneering experience of Elyn Saks, a high-profile law professor who flourished despite her own history of serious mental illness, was directly credited by the compassionate dean of Rose's university as the impetus for promoting, rather than blocking, her efforts to complete her degree. There have been others, including Kay Jamison, a nationally acclaimed psychologist and author who excelled despite serious mental illness. These brave souls risked their careers and their lives to reveal their stories that may benefit others who would face similar circumstances in the future. Apparently, it has worked. Rose's story provides evidence that we may be making progress on this front.

This is why it is so important to continue to highlight the accounts of remarkable people who have triumphed in spite of mental illness. Their positive outcomes can pave the way for the future success of others who will follow. We applaud people like Rose for the courage they have demonstrated in going public with their difficult and painful, yet victorious stories. However, we cannot rest: there is still a long way to go before the stigma of mental illness can once and for all be vanquished.

Carol S. North, MD, MPE, DLFAPA

References:

1. North CS, *Welcome, Silence: My Triumph Over Schizophrenia,* New York: Simon & Schuster 1987 and Avon Books 1989, and Lima, OH: Academic Renewal Press 2002.
2. Jones JTR, North CS, Vogel-Scibilia S, Myers MF, Owen RR, "Medical licensure questions about mental illness and compliance with the Americans with Disabilities Act after the Louisiana Supreme Court Settlement Agreement," Journal of the American Academy of Psychiatry and the Law 2018; 46(4):458-471 (doi: 10.29158/JAAPL.003789-18).

This newsletter was supported in part by a grant from Teva Pharmaceuticals

The US clozapine package insert needs major changes

(continued from page 1)

In 2022, I published an international guideline with 104 authors from 50 countries/regions about personalizing clozapine dosing and titrations.[2] In the spring of 2023, the FDA asked the company in charge for some changes in the package insert. The FDA sent this international guideline to the company. In another e-mail the FDA sent 6 articles on pneumonia, 3 written by me. The company asked for my help with the FDA changes. I spent many hours improving and updating the package insert, but the company told me the FDA rejected all my changes. The FDA rejected my suggestions regarding pneumonia which were based on my 3 published articles which had been sent to the company by the FDA. Instead, the FDA proposed a paragraph on pneumonia that was not based on the literature and was confusing for clinicians.[3]

A Major Step in May 2025

In May 2025, in response to the inaction of the FDA, we published a two-part article proposing that the clozapine package insert needed major changes in the sections on pharmacology[4] and potentially lethal ADRs.[3] The article includes an encyclopedic review of the literature, has 40 authors including most of the US clozapine experts and is supported by 123 letters of recommendation from international experts from 44 countries/regions.

The US Package Insert's Weakness Regarding Basic Pharmacology

In 1989, the manner in which enzymes process drugs, including clozapine, was unknown, so clozapine was introduced with limited studies. Our proposed package insert modifications include:[4]

1) An explanation that clozapine is mainly metabolized by one liver enzyme, called CYP1A2
2) An updated list of drug-drug interactions
3) A warning that infections may decrease CYP1A2 activity and increase the risk of clozapine intoxication
4) A warning that obesity may decrease CYP1A2 activity
5) An acknowledgment that patients of Asian or Native American ancestry have lower CYP1A2 activity and need lower doses
6) A recommendation that personalized titrations with monitoring of a blood protein (c-reactive protein) for inflammation should be considered until prospective studies are available.

The US Package Insert's 5 Boxed Warnings

The first boxed warning concerned agranulocytosis. Over time, the FDA added 3 more boxed warnings for seizures, hypotension, and myocarditis. No other antipsychotics had boxed warnings, but in 2005, the FDA added another boxed warning for all second-generation antipsychotics, including clozapine, regarding the risk of death in elderly patients with dementia.

The FDA has approved the elimination of the hematological monitoring database, but as of today (June 10, 2025), this has not been implemented in the package insert. In our article,[3] we propose that the package insert should focus on saving lives when pneumonia or other severe infections are present, as they kill many more clozapine-treated patients in the US than agranulocytosis.

Apology

I am convinced that, since 2019, thousands of fatal cases of infection in clozapine-treated patients could have been prevented worldwide if the FDA had modified the package insert. Other drug agencies would have followed the example of the FDA. I do not know how to apologize to patients and families of clozapine-treated patients around the world who have suffered or died due to my inability to convince the FDA. At least I would like to apologize to you, the readers of this newsletter. The Trump administration appointed a new FDA Commissioner on April 1 who says that he wants to reform the FDA, but the outcome is currently unknown. I do not know whether or not our two-part clozapine article will have any impact on the FDA. I can only promise you that I will keep trying to modify the US clozapine package insert. Clozapine experts from other countries are hoping for that modification, so they can convince their drug agencies, too.

References:

1. de Leon, J., Ruan, C. J., Schoretsanitis, G., & Kane, J. M. (2020). "Dose and safety concerns of clozapine: Worldwide package inserts need revisions." *Schizophrenia Research*, 216, 2–4. https://doi.org/10.1016/j.schres.2019.12.009
2. de Leon, J., Schoretsanitis, G., Smith, R. L., … Müller, D. J. (2022). "An International Adult Guideline for Making Clozapine Titration Safer by Using Six Ancestry-Based Personalized Dosing Titrations, CRP, and Clozapine Levels." *Pharmacopsychiatry*, 55(2), 73–86. https://doi.org/10.1055/a-1625-6388
3. de Leon, J., Baldessarini, R. J., Balon, R., … De Las Cuevas, C. (2025). "Letter to the FDA Proposing Major Changes in the US Clozapine Package Insert Supported by Clozapine Experts Worldwide. Part II: A Review of Fatal Outcomes in US Pharmacovigilance Data and Proposed Changes." *Journal of Clinical Psychopharmacology*, 45(3), 197–218. https://doi.org/10.1097/JCP.0000000000001990. Freely available.
4. de Leon, J., Baldessarini, R. J., Balon, R., … De Las Cuevas, C. (2025). "Letter to the FDA Proposing Major Changes in the US Clozapine Package Insert Supported by Clozapine Experts Worldwide. Part I: A Review of the Pharmacokinetic Literature and Proposed Changes." *Journal of Clinical Psychopharmacology*, 45(3), 179-196. https://doi.org/10.1097/JCP.0000000000001987. Freely available due to the generosity of the CURESZ Foundation.

Please consider making a donation to the CURESZ Foundation online at CURESZ.org

Your contribution will help provide education and referrals to persons with schizophrenia, their families, and those who work with the seriously mentally ill. CURESZ informs the general public to better understand this serious brain disorder, and to provide scientific advances showing that there is hope for recovery, and a return to a fulfilling and normal life. The CURESZ Foundation is a 501(c)(3) nonprofit organization. All contributions are tax deductible.

"We are committed to helping individuals to cope with and recover from schizophrenia."

You can now also support the CURESZ Foundation by signing up with Kroger Community Rewards.