



Henry A. Nasrallah, MD
Editor-in-Chief

Starting a long-acting injectable antipsychotic soon after a first psychotic episode can prevent a more destructive second episode

For first-episode psychosis, psychiatrists should behave like cardiologists

Schizophrenia has been declared 'arguably the worst disease affecting mankind.'¹

Myocardial infarction (MI) is the leading cause of death in the United States, and schizophrenia is the leading cause of disability. But while cardiologists manage the first heart attack very aggressively to prevent a second MI, we psychiatrists generally do not manage first-episode psychosis (FEP) as aggressively to prevent the more malignant second psychotic episode. Yet abundant evidence indicates that psychiatrists must behave like cardiologists at the onset of schizophrenia and other serious psychosis.

Individuals who survive the first heart attack, which permanently destroys part of the myocardium, are at high risk for a second MI, which may lead to death or weaken the heart so much that heart transplantation becomes necessary. Only implementation of aggressive medical intervention will prevent the likelihood of death due to a second MI in a person who has already suffered a first MI.

Similarly, the FEP of schizophrenia destroys brain tissue, about 10 to 12 cc containing millions of glial cells and billions of synapses.² This neurotoxicity of psychosis is mediated by neuroinflammation and oxidative stress.³ In

most FEP patients, the risk of a second psychotic episode is high, and the tissue destruction of the brain's gray and white matter infrastructure is even more extensive, leading to clinical deterioration, treatment resistance, and functional disability. That is the grim turning point in the trajectory of schizophrenia.

Although most FEP patients respond well to antipsychotic medications and often return to their baseline social and vocational functioning, after a second episode, they are much more likely to become disabled. Unlike physical death, the mental, cognitive, social, and vocational death of chronic schizophrenia goes on for decades with much suffering, misery, and inability to have love and work, which is what life is all about (according to Freud).

MI patients have healthy brains and minds, and they wholeheartedly agree with their cardiologists' recommendations and religiously adhere to their cardiologists' instructions, such as drastic lifestyle changes and a slew of medications intended to lower the risks of a second MI (*Table 1*).

But what is the most common psychiatric practice for a patient who suffers a FEP after he (she) is admitted to an acute inpatient ward? The patient is started on an oral antipsychotic but a long-acting injectable (LAI) anti-


To comment on this editorial or other topics of interest, visit www.facebook.com/CurrentPsychiatry, or go to CurrentPsychiatry.com and click on the "Contact us" link.

psychotic, which is the best protection against future episodes, is never considered, let alone recommended. The patient is given a prescription for an oral antipsychotic at discharge and the family is told to find a private psychiatrist or a community mental health center for follow-up. This practice pattern will likely guarantee a relapse into a second psychotic episode for the following reasons:

- patients' lack of insight (anosognosia) and refusal to believe they are sick or need medications
- adverse effects, especially extrapyramidal symptoms, to which FEP patients are particularly vulnerable unless they are started on small doses
- apathy and lack of motivation to take medication due to negative symptoms, which impair ability to initiate actions (avolition)
- severe memory impairment that leads to forgetting medications
- substance use, such as marijuana, stimulants, and hallucinogens, as well as alcohol, interferes with adherence.

Most patients and families are ignorant about FEP of schizophrenia and its recurrence and devastating effects.

Thus, because of the almost ubiquitous inability to adhere fully to antipsychotic medications after discharge, FEP patients are essentially destined (ie, doomed) to experience a destructive second psychotic episode, whose neurotoxicity starts the patient on a downhill journey of lifetime disability.⁴ LAI antipsychotics are the optimal solution to this serious problem, yet 99.99% of psychiatrists never start LAI during a FEP. This is inexplicable considering the body of evidence that supports early use of LAI to prevent relapse. Of the multipronged strategy that should be used for FEP patients to circumvent a second episode and avoid disability, starting LAI in FEP is the most important interventional

Table 1
Management of a first myocardial infarction

Quit smoking
Change of diet (eg, Ornish diet)
Regular exercise to improve cardiopulmonary fitness
Lower body mass index to less than 25 kg/m ²
Aspirin to prevent thrombus formation
Antihypertensive drugs to control blood pressure
Hypoglycemic drugs to decrease hyperglycemia
Statins to lower low-density lipoprotein cholesterol and triglycerides
Stress management classes

tactic.⁵ Consider the following studies that support initiating LAIs during the FEP:

In South Africa, Emsley et al⁶ conducted the first study of LAI in FEP. In a 2-year follow-up, 64% of patients had complete remission and returned to their baseline functioning with restoration of insight and good quality of life. When the study ended and patients were returned to their referring psychiatrists after 2 years, all patients were switched to oral antipsychotics, because it was the standard practice among psychiatrists there. All patients relapsed within a few months due to poor adherence to oral medications. When they were placed back on the LAI they had received, a sobering (even shocking) clinical finding emerged: 16% of those who had responded so well to LAI for 2 years no longer responded!⁷ This rapid emergence of treatment resistance after only a second psychotic episode demonstrates how the brain changes drastically after a second episode and validates the recent adoption of "stages" in schizophrenia, similar to cancer stages.⁸ Many more patients

Editorial Staff

EDITOR **Jeff Bauer**
SENIOR EDITOR **Patrice Weeks**
ASSISTANT EDITOR **Jason Orsz**
WEB ASSISTANTS
Tyler Mundhenk, Kathryn Wighton

Art & Production Staff

CREATIVE DIRECTOR **Mary Ellen Niatas**
ART DIRECTOR **Pat Fopma**
DIRECTOR, JOURNAL MANUFACTURING
Michael Wendt
PRODUCTION MANAGER **Donna Pituras**

Publishing Staff

PUBLISHER **Sharon J. Spector**
DIGITAL ACCOUNT MANAGER
Reinaldo Valdivia
SENIOR DIRECTOR OF SALES
Tim LaPella
CONFERENCE MARKETING MANAGER
Kathleen Wenzler

Editor-in-Chief Emeritus

James Randolph Hillard, MD

Frontline Medical Communications

CHAIRMAN **Stephen Stoneburn**
PRESIDENT, DIGITAL & CFO
Douglas E. Grose
PRESIDENT/CEO **Alan J. Imhoff**
PRESIDENT, CUSTOM SOLUTIONS **JoAnn Wahl**
SENIOR VICE PRESIDENT, FINANCE
Steven Resnick
VICE PRESIDENT, OPERATIONS **Jim Chicca**
VICE PRESIDENT, AUDIENCE DEVELOPMENT
Donna Sickles
VICE PRESIDENT, CUSTOM PROGRAMS
Carol Nathan
VICE PRESIDENT, CUSTOM SOLUTIONS
Wendy Raupers
VICE PRESIDENT, eBUSINESS DEVELOPMENT
Lee Schweizer
VICE PRESIDENT, HUMAN RESOURCES
& FACILITY OPERATIONS **Carolyn Caccavelli**
VICE PRESIDENT, MARKETING & CUSTOMER
ADVOCACY **Jim McDonough**
VICE PRESIDENT, SALES **Mike Guire**
VICE PRESIDENT, SOCIETY PARTNERS
Mark Branca
CORPORATE DIRECTOR, RESEARCH
& COMMUNICATIONS **Lori Raskin**
EDITORIAL DIRECTOR **Karen J. Clemments**
Subscription Services: (800) 480-4851
In affiliation with Global Academy
for Medical Education, LLC
VICE PRESIDENT, MEDICAL EDUCATION
& CONFERENCES **Sylvia H. Reitman, MBA**
VICE PRESIDENT, EVENTS **David J. Small, MBA**

FRONTLINE
MEDICAL COMMUNICATIONS
7 Century Drive, Suite 302
Parsippany, NJ 07054
Tel: (973) 206-3434
Fax: (973) 206-9378
www.frontlinemedcom.com

Published through an
educational partnership
with Saint Louis University



Table 2

Management of a first psychotic episode

Hospitalize the patient and then initiate an atypical oral antipsychotic as soon as possible to reduce the duration of untreated psychosis
Start a long-acting injectable antipsychotic at least 1 week before discharge. Enroll in the pharmaceutical company's patient assistance program if the family cannot afford the drug
Have the social worker invite a case manager from the local community mental health center to ensure continuity of care and outpatient follow-up
Urge the patient to abstain from all drugs of abuse that can trigger or exacerbate psychosis
Provide diet and exercise counseling to control possible weight gain and to improve hippocampal neurogenesis and functioning

As psychiatric practitioners, we must be clinically aggressive during the 'FEP window of opportunity'

will develop treatment resistance after subsequent episodes.

Subotnik et al⁹ compared LAI vs oral risperidone in 86 FEP patients. At the end of 1 year, they reported a 650% higher relapse rate in the oral medication group compared with the LAI group (33% vs 5%).⁹ This well-done study is a wake-up call for psychiatrists to help FEP patients avoid a brain-damaging second episode by using LAI as a first-line option in FEP.

In a separate study, Subotnik et al¹⁰ reported that when the blood level of a patient receiving an antipsychotic is measured at the time of discharge from FEP and every month for a year, all it took for a relapse was a drop of 25%.¹⁰ Thus, skipping an antipsychotic just 1 day out of 4 (partial nonadherence) is enough to cause a psychotic relapse.

So what should psychiatrists and nurse practitioners do to protect FEP patients from losing their lives to the permanent disability that begins with a second psychotic episode? They must simply change their attitude and their old-fashioned (antiquated?) prescribing habits that keep failing, and start administering LAI during the initial hospitalization right after a few (usually 3 or 4) days of receiving oral antipsychotics (with nursing-assured

swallowing of pills) (*Table 2*). By starting the patient with oral antipsychotics, the presence of an allergic reaction is ruled out, and efficacy onset begins within 2 to 3 days.¹¹ LAI can then be administered several days before discharge and continued in the outpatient setting.

However, various essential psychosocial interventions should be provided along with LAI to ensure progress toward remission and functional recovery after an FEP. The recently published National Institute of Mental Health-sponsored RAISE study¹² is a prime example of the synergy between a multimodal and multidisciplinary team-based approach and antipsychotic medication to improve outcome and quality of life after emerging from FEP.

As psychiatric practitioners, we must be clinically aggressive during the "FEP window of opportunity" to avoid a second episode, thereby bending the curve of the downhill trajectory that occurs after second episodes. We must behave like cardiologists, and relentlessly protect patients who suffer a first "brain attack" from experiencing a relapse. No doubt, any psychiatrists who have a family member with FEP would channel their inner cardiologist and implement the evidence-based

recommendations described above. But then, shouldn't we apply the same standard of care to every FEP patient we see?



Henry A. Nasrallah, MD
Editor-in-Chief

References

1. Where next with psychiatric illness? *Nature*. 1988;336(6195):95-96.
2. Cahn W, Hulshoff Pol HE, Lems EB, et al. Brain volume changes in first episode schizophrenia: a 1-year follow-up study. *Arch Gen Psychiatry*. 2002;59(11):1002-1010.
3. Monji A, Kato TA, Mizoguchi Y, et al. Neuroinflammation in schizophrenia especially focused on the role of microglia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;42:115-121.
4. Alvarez-Jiménez M, Parker AG, Hetrick SE, et al. Preventing the second episode: a systematic review and meta-analysis of psychosocial and pharmacological trials in first-episode psychosis. *Schizophren Bull*. 2011;37(3):619-630.
5. Gardner KN, Nasrallah HA. Managing first-episode psychosis: rationale and evidence for nonstandard first-line treatments for schizophrenia. *Current Psychiatry*. 2015;14(7):33,38-45,e3.
6. Emsley R, Oosthuizen P, Koen L, et al. Remission in patients with first-episode schizophrenia receiving assured antipsychotic medication: a study with risperidone long-acting injection. *Int Clin Psychopharmacol*. 2008;23(6):325-331.
7. Emsley R, Oosthuizen P, Koen L, et al. Comparison of treatment response in second-episode versus first-episode schizophrenia. *J Clin Psychopharmacol*. 2013;33(1):80-83.
8. McGorry P, Nelson B. Why we need a transdiagnostic staging approach to emerging psychopathology, early diagnosis, and treatment. *JAMA Psychiatry*. 2016;73(3):191-192.
9. Subotnik KL, Casaus LR, Ventura J, et al. Long-acting injectable risperidone for relapse prevention and control of breakthrough symptoms after a recent first episode of schizophrenia. A randomized clinical trial. *JAMA Psychiatry*. 2015;72(8):822-829.
10. Subotnik KL, Nuechterlein KH, Ventura J, et al. Risperidone nonadherence and return of positive symptoms in the early course of schizophrenia. *Am J Psychiatry*. 2011;168(3):286-292.
11. Agid O, Kapur S, Arenovich T, et al. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. *Arch Gen Psychiatry*. 2003;60(12):1228-1235.
12. Kane JM, Robinson DG, Schooler NR, et al. Comprehensive versus usual community care for first-episode psychosis: 2-year outcomes from the NIMH RAISE early treatment program. *Am J Psychiatry*. 2016;173(4):362-372.



Have you heard the latest from CurrentPsychiatry.com?

CURRENT PSYCHIATRY's Multimedia Library (mdedge.com/currentpsychiatry/multimedia) contains audio commentary and insight from our authors and others on a range of psychiatric topics, such as:

- Excessive daytime sleepiness
- Malingering
- Are E-cigarettes effective for smoking cessation?
- Psychosis in borderline personality disorder
- Treating tardive dyskinesia
- Clinical rating scales

In these free 3- to 5-minute audiocasts, psychiatry's leading voices elaborate on key points from their **CURRENT PSYCHIATRY** articles, providing you with practical, evidence-based information that emphasizes up-to-date solutions to common clinical problems.

Visit the **CURRENT PSYCHIATRY** Multimedia Library at
<http://www.mdedge.com/currentpsychiatry/multimedia>