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Preventing brain damage in psychosis

I read with great interest Dr. Nasrallah's editorial, "FAST and RAPID: Acronyms to prevent brain damage in stroke and psychosis" (From the Editor, Current Psychiatry, August 2018, p. 6-8). It makes me wonder about the ethics of allowing patients with active psychosis to participate in placebo-controlled studies. If a patient's brain undergoes damage while psychotic, allowing the psychosis to continue without active treatment sounds possibly at odds with a physician's oath. If a patient is in the placebo arm, then they are not receiving treatment for their psychotic symptoms. I wonder about his opinion on this.

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Thank you, Dr. Nasrallah, for your incisive thinking and for bringing our attention as psychiatrists to the crucial issues of our clinical practice. I'd like to offer some nuance on the RAPID acronym. First, I'd like to counter-propose DASH: Delusions, Auditory hallucinations, Strange behavior, Hospital now. This is more in line with getting physicians to tune in to the symptoms that should alarm them and bring them to action. I agree that neurodegeneration and illness recurrence are the problems to address. One unsettled issue remains: With early intervention, can we eventually taper patients off antipsychotics to spare them the metabolic and immune morbidity associated with these medications? There is some evidence that this is possible, but it is difficult to collect data. One of the factors delaying treatment, other than lack of recognition, is the general public's belief that the treatment is sometimes worse than the disease. If we can address this issue in a nuanced fashion, we may get more "early adopters" of these neuron-sparing treatments.

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Dr. Nasrallah is right to focus on brain injury patterns, including inflammation and de-myelination, during psychotic episodes. He and Dr. Roque note that starting a patient on a long-acting injectable antipsychotic as soon as possible may prevent subsequent relapse and further brain damage. However, their editorial omits 2 treatments—minocycline and clemastine—that can help stop CNS inflammation, reduce brain damage, and promote remyelination.

Minocycline has been shown to reduce stroke infarct penumbra size and improve outcomes in functional recovery from stroke.[1,2] Minocycline's effects as a potent CNS anti-inflammatory and antiapoptotic agent are well established.

Clemastine has been shown to improve function in multiple sclerosis by activating oligodendrocyte precursor cells into active agents of myelination and fiber bundle stabilization.[3] Clemastine reverses acute leukoencephalopathy.[4]

If we are to treat acute psychosis as a neurologic emergency, we cannot rely on long-acting injectable antipsychotics as the sole treatment. Psychiatric medication alone is not sufficient across every neuropsychiatric condition in which inflammation and white matter damage are part of the etiology, destruction, and pattern of relapse.

The adverse effects risk of adjunctive minocycline and clemastine is low compared with the potential benefits of stopping inflammation, reducing apoptosis, and jump-starting white matter repair. Doses of oral minocycline in the 50- to 100-mg/d range and oral clemastine in the 1.34- to 2.68-mg/d range together can lead to reduced cranial heat, improved cranial suture mobility, and improved elasticity of white matter bundle tracts palpable on physical examination. Both medications show clinical results in improved emotional self-regulation, according to family reports and clinical observations in the outpatient setting. There is no reason to delay neurologic-based

adjunctive treatment when our goal is to prevent and reverse brain damage.

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Dr. Nasrallah responds

Thanks to my colleagues, Drs. Diamond, Glaser, and Kerlinsky, for their cogent letters about my editorial.

To Dr. Glaser: The "ethics" of conducting placebo-controlled studies when developing a new antipsychotic has been raging for some time. For decades, the FDA has insisted on using a placebo group because around 25% to 30% of research participants respond to placebo, and because participants receiving placebo also complain of many adverse effects. So a new drug has to demonstrate a statistically higher efficacy than a placebo, and the adverse effect profile of the placebo group will put the safety and tolerability profile of a new drug in proper perspective. However, in Europe, they do not conduct placebo-controlled studies; instead, they conduct what is called a "non-inferiority" trial of a new antipsychotic compared with a well-established antipsychotic.

Interestingly, even though the discovery of the neurodegenerative effects of untreated psychosis was only 20 years ago (in 1997 after serial MRI scans revealed progressive atrophy), in the 1960s, the first antipsychotic, chlorpromazine, was compared with placebo in a large national study for 6 months. This study showed without a doubt that chlorpromazine has a higher efficacy than placebo. After the study was done, Dr. Philip May at University of California, Los Angeles looked at what happened to the psychotic patients who received placebo for 6 months and found that they became less responsive to treatment, were re-hospitalized more often, and had more negative symptoms and a poorer overall outcome. That was a clue that untreated psychosis can be harmful, and it supports your point about the ethics of using placebo. In contemporary studies, a trial of oral antipsychotics is 6 weeks, not 6 months. In the year-long, placebo-controlled studies of injectable antipsychotics in stable patients, those who show the slightest increase in delusions, hallucinations, or suicidal/homicidal behavior were promptly taken out of the study and treated. This reduced the "harm," although not completely. Perhaps the FDA will change its policies and adopt the non-inferiority model. That's what is done with nonpsychiatric disorders such as pneumonia, stroke, or diabetes. But one last fact has to be stated: The placebo response in anxiety, depression, or psychosis is much higher (25% to 35%) than the 1% placebo response in pneumonia.

To Dr. Diamond: I really like DASH, and it is an acronym for quick symptomatic diagnosis. Speedy treatment then follows with the acronym RAPID to prevent brain damage that gets worse with delay.

As for the second issue of tapering off the antipsychotic medication, the evidence is overwhelming in favor of continuous pharmacotherapy. Just as hypertension and diabetes will return if medications are tapered or stopped, so will psychosis, and vengefully so because treatment resistance increases with each relapse.[1] This is also true for bipolar disorder recurrences.[2] A recent 20-year follow-up study showed that stopping antipsychotic treatment is associated with a much higher mortality rate than continuation therapy.[3] Another 7-year study showed the same thing.[4] It is literally deadly, and not just neurodegenerative, for persons with schizophrenia to stop their medications.

To Dr. Kerlinsky: I agree with you about using certain adjunctive pharmacotherapies for acute psychosis, which is associated with neuroinflammation, oxidative stress, and neuropil and myelin damage. I support using agents with anti-inflammatory effects (such as minocycline and omega-3 fatty acid), antioxidant effects (such as N-acetylcysteine), and neuroprotective effects (such as minocycline, clemastine, lithium, vitamin D, erythropoietin, etc.). I refer you to my past editorial, "Are you neuroprotecting your patients? 10 Adjunctive therapies to consider,"[5] in which I mentioned all the above. I also pointed out the many neuroprotective effects of atypical antipsychotics in another editorial.[6] Although off-label, those supplements can be useful interventions that can ameliorate the gray and white matter damage associated with acute psychotic relapses in patients with schizophrenia.

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