Henry A. Nasrallah, MD
Editor-in-Chief

Thick chart syndrome
Treatment resistance is our greatest challenge

We all have patients with thick charts, the mentally ill individuals who push our clinical skills to the limit. They respond poorly to the entire algorithm of approved medications for depression, anxiety, or psychosis. Their symptoms hardly budge despite multiple psychotherapeutic interventions. They lead lives of quiet desperation and suffer through many hospitalizations and outpatient visits. They are perennially at high risk for harm to self or others. They get many side effects yet meager benefits from pharmacotherapy. Their social and vocational functions often are minimal to nil. Their life has little meaning beyond doleful patienthood.

Too complicated to be managed by primary care providers and most mental health practitioners, treatment-resistant patients often have several psychiatric comorbidities—both axis I and II. They frequently suffer from axis III disorders as well. Their lack of tangible response (let alone remission) frustrates us. Their poor treatment course and outcomes eventually tempt us to resort to unapproved polypharmacy and other nonevidence-based practices in a desperate effort to help them.

We worry about our persistently unimproved patients; they haunt our thoughts after work. They are a constant reminder of how critical it is for our field to conduct aggressive, relentless research to unravel the underlying biology of chronic nonresponsive, disabling psychiatric brain disorders that rob children, adults, and elderly persons of their potential or even the ability to pursue happiness. We long for treatment breakthroughs that may reverse the downward spiral of their tortured lives.

Treatment resistance in my long-suffering patients incites me to ask important questions that beg for answers, such as:

- Are treatment-resistant patients afflicted by a categorically different subtype of illness, or do they suffer from a more severe form of the illness (ie, a dimensional difference)?
- Are some treatment-resistant patients victims of misdiagnosis? Do

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Effective solutions for treatment-resistant patients can be substantially cost-effective for society at large

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they have a psychiatric illness secondary to an unrecognized general medical condition that fails to respond to standard psychiatric treatments (such as a lack of response to several antidepressants in a patient with hypothyroid-induced depression or lack of efficacy of neuroleptics in psychosis secondary to a porphyria or Niemann-Pick disease)?

- Why isn't the pharmaceutical industry conducting trials that target treatment-resistant patients? Controlled research trials in all clinical drug development programs for psychotropic medications explicitly exclude patients with a history of nonresponse. Thus, if a drug proves to be superior to placebo in FDA trials, it is likely to have efficacy in responsive patients but not in patients who have a history of nonresponse to prior medications.
- Why are there no FDA studies of combination therapy—using drugs with different mechanisms of action—jointly sponsored (where necessary) by 2 or more pharmaceutical companies? Evidence-based, FDA-approved combinations are common for severe hypertension, diabetes, and cardiovascular disease; why not for severe psychiatric disorders?
- Why are personality disorders and psychiatric comorbidities more likely in treatment-resistant patients, and is this a neurobiologic clue for our nosologic/diagnostic framework and an impetus for better and innovative drug development?
- Why isn't more funding from the National Institute of Mental Health targeting treatment-resistant diagnostic groups? Effective solutions for treatment-resistant populations, whose care often is very expensive, can be extremely beneficial for the affected individuals as well as substantially cost-effective for society at large.

Until my questions can be answered—and better treatment options emerge for my treatment-resistant patients—I will continue to do my best to relieve their agony and anguish. I will then write more progress notes and add yet more sheets of paper to their already thick charts.

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Published through an educational partnership with University of Cincinnati