The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column gave informed consent for the publication of the column.

N-Acetylcysteine augmentation in refractory obsessive–compulsive disorder

Sreenivasa Bhaskara, MD

A 25-year-old man was referred to our clinic with a diagnosis of nonverbal learning disorder and obsessive–compulsive disorder (OCD) made at age 12 years. His OCD symptoms included checking and ordering rituals, symmetry, washing and self-care rituals. He spent 8–10 hours each day on self-care and toilette routines, continuing until it felt "just right" and the feeling of "incompleteness" would go away. Past treatments included adequate trials of selective serotonin reuptake inhibitor (SSRI; fluvoxamine, fluoxetine and paroxetine monotherapy with limited response). Augmenting the SSRI with risperidone and quetiapine and concurrent outpatient psychotherapy involving cognitive behavioural (CBT) and acceptance and commitment (ACT) paradigms was ineffective. A 3-month admission to a specialized residential program for OCD, where the patient received a combination of up to 250 mg of clomipramine (level 2320 nmol/L) and intensive CBT, showed a partial response that was not sustained.

When the patient came to us, he was on clomipramine 150 mg/d and aripiprazole 2 mg/d. His Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) score was 34 (extreme), and his functioning was substantially impaired. He was unemployed, living with his parents, had no social life and was house-bound for the most part. *N*-Acetylcysteine (NAC) 1000 mg twice daily was added and increased to 1500 mg twice daily a week later. It was very well tolerated, with no reported adverse effects. The patient noticed some changes at week 4 and felt hopeful. At week 12 there were substantial improvements (Y-BOCS score of 28), and he was able to limit his rituals to less than 3 hours a day. His clomipramine was reduced to 75 mg/d owing to anticholinergic effects and sedation, with no worsening of his obsessions or compulsions. He continued on clomipramine 75 mg/d, aripiprazole 2 mg/d and NAC 3000 mg/d, and at 6-month review his condition remained substantially improved (Y-BOCS score of 18). His functioning also improved substantially over the ensuing months. He managed to obtain his driver's license and started part-time work. One year later, the patient has continued to do well; he is employed full time and intends to start a university degree.

Obsessive–compulsive disorder is a disabling neuropsychiatric disorder, and the evidence for serotonergic dysfunction in its pathophysiology is well established. Most clinical practice guidelines recommend serotonergic antidepressants as first-line therapy.[1,2,3] However, response rates are incomplete, and up to 40%–60% of patients do not respond to serotonergic agents.[4] The etiology of OCD and related conditions remains elusive, and they are best conceptualized as a heterogeneous group of disorders with a complex neurobiology beyond serotonergic dysfunction. One of the postulated neurobiological mechanisms involves abnormal glutamate metabolism, and in keeping with this hypothesis, there have been a number of glutamate-modulating medications studied in the treatment of OCD.[5] *N*-Acetylcysteine is the *N*-acetyl derivative of the amino acid L-cysteine with diverse postulated mechanisms of action involving glutamate transmission, glutathione and oxidative homeostasis, cytokine and anti-inflammatory-mediated pathways, and dopamine modulation among others.[6] It has been studied in the treatment of a wide range of neuropsychiatric disorders, such as schizophrenia, bipolar disorder, autism, addiction and Alzheimer disease.[7] There is conflicting but encouraging evidence for NAC as an adjunct treatment in the psychopharmacological management of treatment-refractory OCD.[8,9,10] In a recent systematic review on the efficacy of NAC in OCD, Cousto and Moreira[11] summarized the pooled evidence to date from 3 case reports, 2 case series (n = 11) and 5 randomized controlled trials (n = 210). All 3 patients in the case reports and 5 of 11 patients in the case series showed a positive response. Four of the 5 clinical trials were also favourable for NAC as a promising treatment option. The authors concluded that despite the methodological limitations of current trials, heterogeneity of participants, many unanswered questions about the optimum dosage and duration, absorption and bioavailability of NAC and other factors, the overall trend, nonetheless, was in favour of NAC over placebo as a potentially useful but underestimated treatment option. *N*-Acetylcysteine was well tolerated, and the most common adverse effect was gastrointestinal. Our patient responded very well to augmentation with NAC with no adverse effects, and the improvements have been sustained for more than a year, making a placebo response or spontaneous recovery less likely. In refractory OCD, where treatment options are limited and response is partial at best and accompanied by substantial adverse effects, the generic availability, low cost and favourable tolerability profile make NAC a promising augmentation strategy in at least a subgroup of patients.

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