Successful Treatment of Major Depressive Disorder With Add-On Buprenorphine in a Patient With Previous Nonresponse to Standard Antidepressants

To the Editor: Major depressive disorder (MDD) is a global mental health problem that affects people of all ages, negatively impacting their personal, academic, social, and family life.[1] Prominent symptoms are depressed mood and loss of interest or pleasure in almost all activities most of the day (*DSM-5* criteria).[2] About 65% of MDD patients show inadequate response to initial treatment.[3–5] Increasing evidence[6–8] supports the hypothesis that mood disorders involve a dysregulation of the endogenous μ- and kappa-opioid system, and endorphin deficiency seems to play a role in suicidality.[9–11] Buprenorphine is a central-acting partial μ- and kappa-opioid receptor agonist.[12,13] A growing number of studies[7] support using buprenorphine to treat MDD symptoms. However, use of opioid agonists for treating MDD in clinical practice is restricted because of unresolved issues of abuse and dependence.

Case report. A 40-year-old woman was admitted to our psychiatric clinic with an 11-year history of recurrent MDD. Psychopathologic symptoms at admission were depressed mood, loss of drive, nonspecific anxiety, and insomnia. Her antidepressant medication included tranylcypromine 20 mg/d and trimipramine 200 mg/d. A diagnosis of severe persistent MDD according to *DSM-5* criteria was established since the MDD symptoms reemerged 2 years ago. She had a family history of MDD in her father and schizoaffective disorder in her sister.

Cranial magnetic resonance tomography and laboratory findings including cerebrospinal fluid analysis were unremarkable. There was no history of substance use. Since her first MDD episode in 2005, she had been treated 13 times in the inpatient setting. During the last few years, she had received almost all available antidepressants (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic and tetracyclic antidepressants, and monoamine oxidase inhibitors) in sufficient doses and durations combined with antipsychotics (as augmentation strategy) or lithium. Repetitive transcranial magnetic stimulation (rTMS) had no effect, and continuous vagus nerve stimulation (VNS, implanted in 2012) showed no significant mood-stabilizing function. She had received multiple sessions of electroconvulsive therapy (ECT) since 2011. We performed 7 ECT sessions with insufficient response. After receiving written informed consent from the patient, we started an off-label therapy trial with buprenorphine 0.2 mg sublingual in addition to current antidepressant treatment. Within a few days, there was a clinically significant improvement in mood, drive, and anxiety. The Beck Depression Inventory[14] score improved from 47 to 18 within 1 week. We observed no side effects.

This case shows a clinically meaningful antidepressant effect of buprenorphine in a patient with therapy-resistant MDD who did not respond sufficiently to oral antidepressants, VNS, rTMS, or unilateral and bilateral ECT. Uncontrolled naturalistic clinical trials[15,16] have described the efficacy of low-dose treatment with opioids, including buprenorphine, for treatment-refractory MDD. A newly published multicenter, randomized, double-blind, placebo-controlled, 2-stage sequential parallel comparison study[17] was conducted in adults with MDD who responded insufficiently to 1 or 2 courses of antidepressants. Participants were randomly assigned to receive adjunctive treatment with 2 mg/2 mg of buprenorphine/samidorphan, 8 mg/8 mg of buprenorphine/samidorphan, or placebo. Significant symptom improvement was shown in the 2/2 dosage group across the 3 depression outcome measures between onset and the end of the 4th week of treatment for response and remission.[17] A 1-week pilot trial[18] in patients with treatment-resistant MDD during a placebo-controlled crossover trial was performed to assess the opioid pharmacodynamics profile following escalating doses of samidorphan coadministered with buprenorphine in opioid-experienced adults. Following the 1-week trial, the ratio associated with maximum antagonism of opioid effects exhibited significant improvement in 17-item Hamilton Depression Rating Scale and Montgomery-Asberg Depression Rating Scale scores.[18]

Buprenorphine might be a promising candidate for treatment of MDD in patients who do not respond to standard antidepressants.

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Mohamed Elsayed, MD[a]
mohamed.elsayed@uni-ulm.de
Maximilian Gahr, MD[a]
Bernhard J. Connemann[a]
Carlos Schönfeldt-Lecuona, MD[a]

[a]Department of Psychiatry and Psychotherapy III, University of Ulm, Leimgrubenweg, Ulm, Germany

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