

Off Label Use of Suboxone for Treatment Resistant Depression

George Kamajian¹, Robert Cable², Jonathan Greco², Brady Laughlin² and Tanya deGroot²

¹Largo Clinic, 10500 Ulmerton Rd, Suite 360, Largo, 33771 FL, USA

²Lake Erie College of Osteopathic Medicine, 5000 Lakewood Ranch Blvd, Bradenton, 34211 FL, USA

***Correspondence to:**

George Kamajian, DO
Largo Clinic
10500 Ulmerton Rd, Suite 360
Largo, Florida 33771, USA
Fax: +1 727 595 5392
E-mail: beachdoc1@gmail.com

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Dear Editor,

Major Depressive Disorder (MDD) is a condition that affects approximately 12% of the population [1] and recurs at a rate between 50-85% regardless of treatment [2]. Treatment resistant depression (TRD) is considered if patients do not show alleviation of depressive symptoms after at least two trials of antidepressants from different pharmacologic classes [3]. Current antidepressant therapies which modulate serotonin, norepinephrine, and dopamine are based on the monoamine hypothesis, but the mechanism of MDD is now known to be more complex [4]. More aggressive treatment options including ketamine infusions, deep brain stimulation, and magnetic seizure therapy [5, 6] have also been applied in attempts to influence the unknown areas of our understanding of depression. Opiates have been known to influence feelings of depression since the 1950s. Previous studies have identified potential antidepressant effects of buprenorphine. Buprenorphine is a special type of opiate medication that is a partial agonist at the mu receptors, an antagonist at the kappa receptors and has affinity for the delta receptors, all potential modulators of mood. Recent data by Falcon et al. suggests the Kappa opioid receptors are a key player mediating the effects of BPN in tests sensitive to antidepressant drugs in mice [7]. The introduction of opioids with mixed agonist-antagonist with reduced dependence and abuse profiles has made possible the reevaluation of opioids for depression [8]. Buprenorphine has a low side-effect profile and is safe for use in the elderly and patients with renal dysfunction [9]. Buprenorphine alone has the risk of abuse like other opiates, but this can be prevented by the addition of naloxone in combination.

Between 2008-2012 the Largo Clinic in Largo, Florida conducted an open-label trial using low-dose buprenorphine/naloxone for patients meeting the criteria for TRD. Our clinic focuses on the medical needs of the uninsured and underinsured of our catchment area. Of our total patient population at the Largo Clinic, 30% present as opioid dependent, specifically for our opioid addiction program in which Buprenorphine is the mainstay of treatment. Of 25 patients initially enrolled, 20% were opioid naïve and 80% were non-naïve. Patients ranged from 21 to 63 years old. These individuals presented at our clinic for the substance abuse program or general medical treatment. Suboxone was offered when issues of treatment-resistant depression were recognized either at initial presentation or at the time of their exit interviews from the addiction program. It is not uncommon for mental health professionals in our area to have a six month waiting list or more. This timeline is easily doubled when patients do not have insurance coverage, leaving many of these patients to seek other illicit chemical means of depression reduction. All our patients had tried at least 3 different antidepressant medications without success prior to enrollment with our clinical trial. Suboxone strips were initiated at 2 mg per day and response was measured using the Hamilton Rating Scale for Depression (HAM-D). Dosage was titrated based on response with a treatment range between 0.5 and 8 mg per

day, with an average therapeutic dosage of 2 mg per day. The open enrollment period was one year. Data was evaluated at one, two and four years. Of the initial patients enrolled, 90% maintained monthly office visits and had negative monthly urine toxicology screens throughout the data collection period. Of patients who transferred out of our office and were on Suboxone therapy for depression, 75% requested maintenance of this therapy from alternate practitioners. Most returned to our office to continue off-label use buprenorphine. Of our initial cohort of patients, 50% have maintained their relationship with us since initiation of off-label buprenorphine therapy (2008) until the present (2016). At the end of the trial all patients showed significant improvement based on the HAM-D scale, and reported reduction of feelings of depression, fatigue, and hopelessness. These effects were observed within 48 hours of initiation of treatment and continued throughout the trial. None of the patients stopped treatment based on any side effects.

Our findings are supported by the Karp et al. article, Safety, Tolerability, and Clinical Effect of Low-Dose Buprenorphine for Treatment-Resistant Depression in Mid-Life and Older Adults [9], which demonstrated that buprenorphine can realistically be considered as a new approach to managing TRD (This trial was conducted to address the issue that the majority of middle age to older adults failed treatment when using traditional monoaminergic medications). The authors wanted to address the lack of evidence-based data to support the use of buprenorphine as an alternative pharmacotherapy for TRD. This study showed a significant decline in depression severity over the course of the study and an increase in depression levels once the buprenorphine was discontinued.

What we have observed with our study population at Largo Medical Clinic, and seen in Karp et al.'s clinical trial, supports the use of low-dose buprenorphine, or the combination of buprenorphine/naloxone as a legitimate pharmacological treatment of TRD. Long-term clinical trials on this topic are necessary to provide us with more evidence-based recommendations, and we encourage the investigation of buprenorphine/naloxone for use in TRD in the future.

Based on the findings of our retrospective study, we suggest further research for Suboxone in the field of depression and mood disorders. However, we also suggest caution with the use of Suboxone in high risk individuals as pointed out by Blum et al. in their article Genetic Addiction Risk Score (GARS): molecular neurogenetic evidence for predisposition to Reward Deficiency Syndrome (RDS) [10]. In the future, we recommend that individuals be screened for reward deficiency syndrome and the likelihood of substance abuse disorder prior to initiation of Suboxone treatment for mood disorders. However, it should be duly noted that individuals were not risk stratified for substance abuse disorder in our study

because many were already suffering from opioid addiction and dependent-type behaviors, and as mentioned earlier, a patient population that is either not or underinsured, made genetic screening not a viable financial option for this study. Another limitation of the study was the use of the HAM-D for measurement of depression. Though at one time considered the gold standard, it places a stronger emphasis on insomnia and less emphasis on suicidal ideation, which may be more accurately measured with other scales (e.g. Beck Depression Index or Montgomery-Åsberg Depression Rating Scale).

Regards,

George Kamajian, D.O.

Robert Cable, MS IV

Jonathan Greco, MS IV

Brady Laughlin, MS IV

Tanya deGroot, MS IV

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