Dr. nat. med. Maxine Dibué-Adjei

Director Medical Affairs Neuromodulation Europe

Dario Mirski MD

Vice President of Medical Affairs Neuromodulation

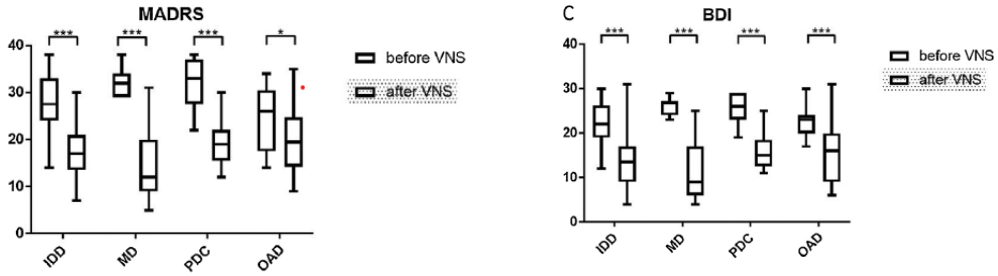
we were happy to discover the ILAEs effort to create clinical practice guideline for treatment of depression in adults with epilepsy. It is a crucial topic in epilepsy management and the availability of practical guidelines will surely improve patient care on a wide level. As manufacturer of vagus nerve stimulators (VNS) for drug-resistant epilepsy (DRE) and treatment resistant depression (TRD), we would like to provide some comments on the section of the draft on VNS.

The draft currently states:

"Despite a large number of studies has investigated the effect of VNS on symptoms of depression in people with epilepsy, no studies have investigated the efficacy of VNS on patients with epilepsy and a diagnosis of depression at baseline as the primary outcome"

In their 2019 publication Spindler et al report on the effect of VNS on depressive symptoms in patients with DRE[1]. All patients receiving a VNS for DRE at Charité Hospital between 2003 and 2014 in Berlin were prospectively screened for mood disorders by Dr Kathrin Bohlmann, consultant psychiatrist and psychotherapist. Dr Bohlmann performed a MADRS assessment of all 80 patients and diagnosed mood disorders in 74% of DRE patients later receiving a VNS: there were 33 cases of interictal dysphoric disorder, 12 cases of major depression, 10 cases of personality disorder cluster, and 20 cases of organic affective disorder.

We are understand that the guidelines focus on major depression (MD) only and not inter-ictal dysphoric disorder, due to it's unclear nosology, however the Spindler paper does report on a small group of patients with MD. These patients with MD showed the most severe pre-implant MADRS and BDI scores but also showed the greatest improvement under VNS Therapy: from 32 to 16 ($p < 0{,}001$) in MADRS and from 26 to 13 ($p < 0{,}001$) in BDI.



[1] Spindler et al Seizure 2019 Jul;69:77-79.

Furthermore, the draft currently states:

In general, the electrical "dose" is lower for depression than for refractory epilepsy but no protocols are available (48)."

The article 48 referenced here is a review article by Conway et al that in turn refers to the D-21 trial which was published as Aaronson et al 2013[2]. This was a double-blinded dosing trial in which TRD patients were randomized to either "low", "medium" or "high" VNS doses in the acute phase. Although the "high" group displayed a median output current of 1.5 mA (which is at the lower end of the therapeutic range for epilepsy), doses of up to 2.5 mA were used in the long-term phase of the study (See Table 62 from the indications for use of VNS Therapy System). Higher ranges were not chosen in the acute phase also considering the fact that some patients cannot tolerate higher output currents and therefore would have failed the randomization process.

Aaronson et al 2013 study found a negative correlation between total charge delivered per day and depressive symptoms in BDI, suggesting greater antidepressant efficacy at higher doses. To our knowledge there is no study that suggests that the antidepressant effect of VNS can be elicited by lower levels of stimulation than the antiepileptic effect. From a mechanistic point of view, sufficient brainstem activation appears to be necessary for both effects and is dependent on the amount of fibers in which action potentials can be elicited. This in turn is mostly dependent on the output current applied to the nerve.

We are aware that some leading experts state that lower stimulation doses should be used to treat depression than to treat epilepsy, however to our knowledge there is no data to support this and in fact more data to support the contrary (Aaronson et al 2013). We do not recommend lower levels of stimulation in our indications for use of our VNS Therapy System for depression[3]. We understand that the rationale for some VNS users to recommend low levels of stimulation may be to avoid induction of manic episodes. Induction of manic episodes by VNS in patients with unipolar depression is rare and occurred in 0.4% of patients in the acute phase of the original VNS for TRD randomized controlled trial[4]. VNS Therapy is also a safe and effective treatment for depressive episodes in patients with bipolar disorder[4],[5], in which experts recommend to increase dosages slowly but to the full therapeutic dose in conjunction with a mood stabilizer.

We believe that it is important to bring attention to this, as this assumption in the past has led to many patients receiving VNS Therapy for depression being under-dosed and therefore not experiencing the full benefit of the therapy.

[2] Aaronson et al Brain Stimul 2013 Jul;6(4):631-40.
[3] VNS Therapy Physician's Manual, LivaNova PLC
[4] Rush et al Biol Psychiatry 2005;58:347–354
[5] McAllister-Williams et al Int J Bipolar Disord. 2020 May 2;8(1):13.

Table 62. Stimulation Parameters at Week 50 of VNS Therapy in the Post-approval (D-21) Study (Safety Population)

Stimulation Parameters*	LOW Median Value at week 50 (Range) N=97	MEDIUM Median Value at week 50 (Range) N=95	HIGH Median Value at week 50 (Range) N=103	TOTAL Median Value at week 50 (Range) N=295
Output current (mA)	1.0 (0.0-2.00)	1.25 (0.0-2.25)	1.50 (0.0-2.50)	1.25 (0.0-2.50)
Frequency (Hz)	20 (1-30)	20 (1-30)	20 (1-25)	20 (1-30)
Pulse width (µsec)	250 (130-500)	250 (130-250)	250 (130-500)	250 (130-500)
ON time (seconds)	30 (30-60)	30 (7-60)	30 (30-60)	30 (7-60)
OFF time (minutes)	5.0 (1-180)	5.0 (0-180)	5.0 (2-180)	5.0 (0-180)

*The magnet output current should be set to 0 mA

We hope that the above points can contribute some additional perspectives on the VNS section.

Best regards,

Maxine Dibué-Adjei

Dario Mirski