NeuroRegulation

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Hemodynamic and Pulmonary Safety Profile of the Accelerated Neuroregulation Procedure

Andre Waismann[1], Albert Kabemba[1], Olga Medowska[1], Robert Salzman[2], Cathy Philpott[3], and Milesh M. Patel[4]*

[1]ANR Clinic, Tampa, Florida, USA
[2]Lakeland Allergy, Asthma and Immunology, Lakeland, Florida, USA
[3]Philpott Healthcare Consulting, LLC, Athens, Tennessee, USA
[4]Janessa Company, LLC, Bristow, Virginia, USA

Abstract

Background. Opioid use disorder (OUD) affects an estimated 26.8 million people globally (Strang et al., 2020). In 2020, opioid overdose visits in the United States increased by 28 percent (Harringa, 2021). Opioid-dependent individuals now comprise an internationally and nationally recognized vulnerable population (Harringa, 2021). Effective, proven, and safe treatments for OUD are needed to improve quality of life and life expectancy and to decrease international and national costs of care for this vulnerable population (Florence et al., 2016). Accelerated neuroregulation (ANR) is an internationally recognized protocol for treatment of OUD and has been utilized for over 20 years in hospitals in Israel, Switzerland, Brazil, Georgia, and other countries. **Methods**. This study is a retrospective review conducted by a team of healthcare providers based on the medical record documentation of patients who underwent the ANR procedure and subsequent follow-up care at the ANR clinic located in Florida. Following review of clinical case data, a comparative of patient hemodynamic and pulmonary stability was selected as the criteria to evaluate the procedure's safety. **Results**. The study assessed a sample group of patients treated with the ANR procedure. The sample group consisted of 50 individuals who underwent the ANR procedure between November 2020 and February 2021. All patients treated during this period were included in the sample size, no exclusions were applied. **Conclusion**. The study analysis demonstrates that ANR procedures are a safe and effective treatment for OUD based on the stability of hemodynamic and pulmonary physiological response data.

Keywords: opioid use disorder (OUD); accelerated neuroregulation (ANR); opioid dependency; opioid dependency treatment; opioid dependency treatment safety; ANR safety; ANR physiological response

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***Address correspondence to**: Olga Medowska, ANR Clinic, 2002 North Lois Avenue, Suite 150, Tampa, FL, 33607, USA. Email: olga@anrclinic.com

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

In 2017, greater than 47,000 individuals in the United States died from opioid related overdoses (Strang et al., 2020). The continually growing opioid addiction epidemic contributes to poor public health and has serious social and economic implications (American Hospital Association, 2020). Estimates from the Centers for Disease Control and Prevention (CDC) indicate that the costs of healthcare and treatment services, decline in productivity, and involvement with the criminal justice system total over $78 billion a year nationally (Florence et al., 2016). Safe and effective treatment services that correct biochemical imbalances and reduce cravings are critical to help combat this drug crisis impacting increasingly vulnerable populations within the U.S. (Florence et al., 2016).

Accelerated neuroregulation (ANR) is a medical therapy for the treatment of opioid dependency and use disorder, a recognized medical diagnosis (Strang et al., 2020). Developed by Israeli doctor and intensive care specialist Dr. Andre Waismann, the treatment protocol addresses opioid dependency by correcting biochemical imbalances that exist

between opioid receptors and endorphins in the central nervous system. The ANR procedure has been successfully applied for over 20 years internationally.

The goal of this retrospective study is to investigate the safety profile of the ANR procedure in a subset of patients from 2020 to 2021. The following data analysis describes the relationships between the ANR procedure and the physiological response to withdrawal (hemodynamic and pulmonary stability).

Background

ANR approaches opioid dependence and addiction from a scientifically based medical perspective. Shah and Hueker (2023) describe the complex nature of neuro-opioid receptors. ANR addresses the following three major key elements responsible for fueling opioid dependence on a neurobiological level:

1. what normal brain function looks like prior to opioid use,
2. the neuroadaptation that occurs from continuously exposing the nervous system to opioids, and
3. how modern medicine can reregulate the endorphin receptor system and return the brain to its pre-drug-dependent state.

The goal of the ANR procedure is to bring the nervous system back into balance by modulating it to decrease receptor production, while allowing the body to resume proper levels of endorphin production. ANR also allows the metabolizing and elimination of unnecessary exogenous opioids from the body. It is in achieving this cellular, neurochemical, and endorphin receptor rebalance that biophysical cravings, which are a hallmark of opioid dependence, are rendered inactive. The ANR procedure method is conducted under deep sedation to avoid the active suffering of opioid withdrawal symptomology, guaranteeing that all patients who undergo the ANR procedure will complete primary treatment and be followed by a period of consolidation treatment orally.

ANR Procedural Intervention

Pretreatment Evaluation. Prospective patients who arrive at the clinic are educated about the safety and effectiveness of the ANR procedure and treatment, including risks and benefits. Clinic staff respond to any questions posed by the patient and provide further clarification as needed. Once the patient consents to ANR treatment, a full medical history is conducted. Inquiries into substance abuse and other medical illnesses, allergies to medications, and anesthesia reactions are documented as noted in Table 1. Patients are screened for social determinants of health, psychosocial concerns, and psychiatric illnesses. Additionally, the patient is assessed for their level of motivation for the treatment and existing support systems.

Based on the patient's medical history, a full physical examination is then completed. If necessary, additional examination may include but is not limited to laboratory studies, electrocardiogram, spirometry, imaging studies, echocardiography, and ultrasonography. This is completed 2 to 3 weeks prior to the ANR procedure. A consultation with an anesthesiologist with critical care medicine expertise is scheduled. The consulting anesthesiologist will then be involved in intubating and administering the anesthetic (moderate to deep sedation) portion of the treatment. At any point in time, additional specialists may be consulted if needed based on the examination and assessment.

Table 1
Potential Risk Factors Associated With ANR Treatment

Type	Risk Factors
Health History	Liver, renal, heart, and lung, and metabolic disorders. Allergies to medications.
Procedural	Prior complications associated with anesthesia. Allergies to anesthesia medications. Complications from the placement of vascular access (thrombophlebitis, Pneumothorax).

Note. ANR = accelerated neuroregulation.

Patients are excluded from treatment if they fall into category IV or V of the American Society of Anesthesiologists (ASA) physical status classification system (ASA, 2020). Patients who fall into category III are also considered for exclusion; however, the decision whether to exclude the patient from ANR treatment is based on anesthesiologist clinical judgment and how well their health has been coordinated by their primary care provider.

If there are no contraindications found in the preevaluations, examinations, assessments, and

consultations, then the patient is admitted to the hospital on the day of procedure and prepared per procedural protocol for the ANR intervention. A final consultation is held one day proximal to the hospital admission.

ANR Treatment Protocol Overview. The ANR procedure protocol includes four treatment steps:

1. In the first 5 hours before onset of anesthesia, medications are administered for regulation and stabilization of the autonomic nervous system as noted in Table 2.
2. After preprocedure medications are given, the patient is intubated and anesthesia with propofol is introduced. Naltrexone administration is then started. Patients receive two to three individually titrated doses of naltrexone over 5 to 6 hours via gastric tube. A circulation-stabilizing and sedating concomitant medication prevents heart, circulatory, respiratory, or cerebral reactions.
3. After the blockade, the endorphin system becomes suppressed. Patients are monitored, assessed, and provided intervention(s) with 1:1 care from the intensive care or anesthesia nursing staff. After the anesthesia and extubation are accomplished, the patient remains in the postanesthesia care unit setting for another 2 to 3 hours for monitoring.
4. During the postacute phase, naltrexone is taken in tablet form during 4 to 12 months of consolidation treatment to ensure success as noted in Table 3.

Table 2

Medications Given Prior to Anesthesia

Medication	Purpose
Benzodiazepine	Reduce treatment day anxiety
Histamine H_2 antagonist (H_2 blocker)	Prophylactic prevention of bronchospasms
Alpha-2 Agonist	Lowers blood pressure and heart rate; providing a cardioprotective physiological state
Vitamin C	Acidifies metabolism; facilitates elimination of opioids from system

Table 3

Consolidation Naltrexone Treatment Parameters for ANR Post Procedure

Length of Opioid Dependency	BMI	Dose of Naltrexone	Duration of Naltrexone Regiment
3 years of less	18.5–24.9	25–50mg	Minimum 4 months
3–7 years	25–29.9	25–50mg	6–12 months
Greater than 7 years	30 or greater	50–75mg	Minimum 12 months

Note. ANR = accelerated neuroregulation; mg = milligrams.

Methods

This study is a retrospective review conducted by a team of healthcare providers based on the medical record documentation of patients who underwent the procedure and subsequent follow-up care at the ANR Clinic located in Florida. Following review of clinical case data, a comparative of patient hemodynamic and pulmonary stability was selected as the criteria to evaluate the procedure's safety.

Study Sample

This study investigated a random sample of patients who underwent ANR procedures between 2020 and 2021. The following provides an overview of data collection processes for the sample.

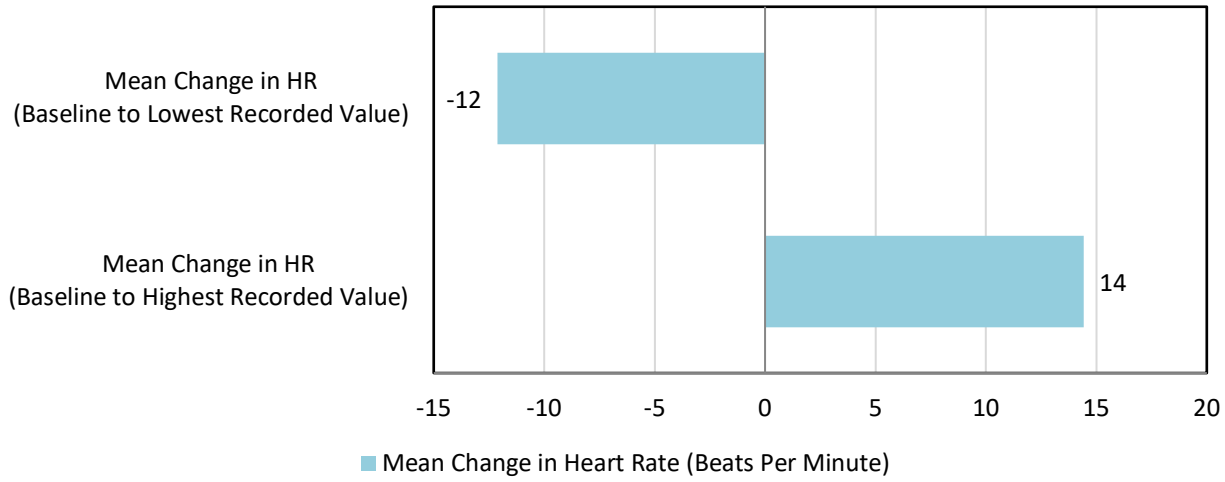
Hemodynamic and pulmonary data were collected on a total of 50 patients who received ANR treatment at the ANR Clinic located in the U.S. in 2020 and 2021. Mean heart rate (HR), systolic and diastolic blood pressure (BP), and oxygen saturation were recorded at baseline, during, and after the ANR procedure. Baseline hemodynamic and pulmonary data were recorded every 15 min upon patient admission to the hospital and prior to induction of anesthesia. At induction of anesthesia, hemodynamic and pulmonary evaluations were recorded every 5 min, and continued until the patient was 30 min postextubation. Once the patient was considered stable, they were transferred to their room for posttreatment care where their hemodynamic and pulmonary data were recorded every 4 hours.

Results and Analysis

Heart Rate Variability During ANR Procedure

To calculate variability, the highest and lowest recorded HR during the ANR procedure for each patient was utilized. Baseline values were subtracted from each of these highest and lowest values and then averaged, respectively, across the sample. Results showed that HR decreased on average by 12 beats per minute (bpm) and increased by 14 bpm from baseline (Figure 1). Since the highest and lowest HR values were used, these averages represent the maximum delta, or change (i.e., upper and lower boundary) from baseline levels. As a result, these data show minimal HR variability during ANR procedure, given that they are still within normal physiological parameters (American Heart Association [AHA], 2021a). Moreover, no adverse events were reported at any interval during or immediately after the procedure and at 1 hour, 2 hours, 4 hours, or 6 hours post-ANR treatment. No variability in hemodynamic and pulmonary data were reported.

Figure 1. *Changes in Mean HR From Baseline During ANR Procedure.*



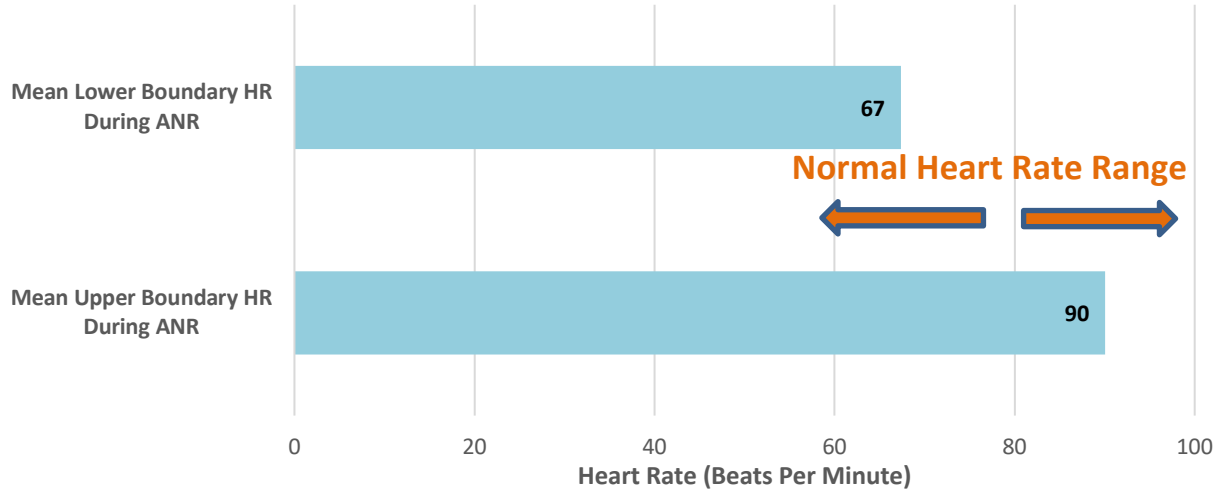
Note. ANR = accelerated neuroregulation; HR = heart rate in beats per minute.

Average lowest and highest HR during the ANR procedures was 67 bpm and 90 bpm, respectively (Figure 2). Additionally, standard deviation for the lowest and highest HR was 12.8 and 10.5, respectively. According to the AHA (2021a), normal HR ranges from 60 to 100 bpm. HR for this sample of patients was within the boundaries of normal parameters (AHA, 2021a). Moreover, incorporating the means associates HR within normal HR parameters. This supports ANR procedure safety as the procedure does not contribute to abnormal HR or reported cardiovascular abnormalities during procedural treatment.

Blood Pressure Variability During ANR Procedure

Similar to HR data, highest and lowest BP values were reviewed for this analysis. Baseline BP was subtracted from each highest and lowest recorded value and then averaged, respectively, across the sample. During ANR procedures, average systolic BP decreased by 26 mm Hg and increased by 13 mm Hg from baseline (Figure 3). Also, average diastolic BP decreased by 18 mm Hg and increased by 9 mm Hg from baseline (Figure 4). Like HR, the mean BP values represent the maximum difference (i.e., upper and lower boundary) from baseline. As a result, these data points also suggest minimal mean systolic and diastolic BP changes during ANR procedures from baseline. Mean upper boundary

Figure 2. *HR Mean During ANR Procedure Compared to Normal Physiologic Range.*

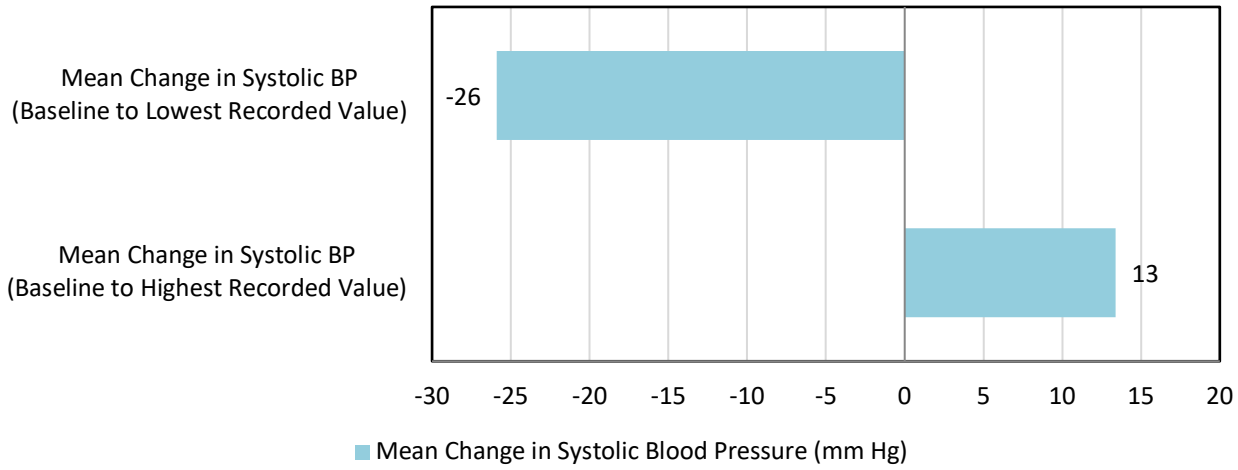


Note. ANR = accelerated neuroregulation; HR = heart rate in beats per minute.

diastolic BP during ANR procedures was within normal range (Figure 5) and BP normalized posttreatment (Figure 5). These data points suggest that while BP increases during treatment, the ANR procedure does not alter long term hemodynamics in any adverse way.

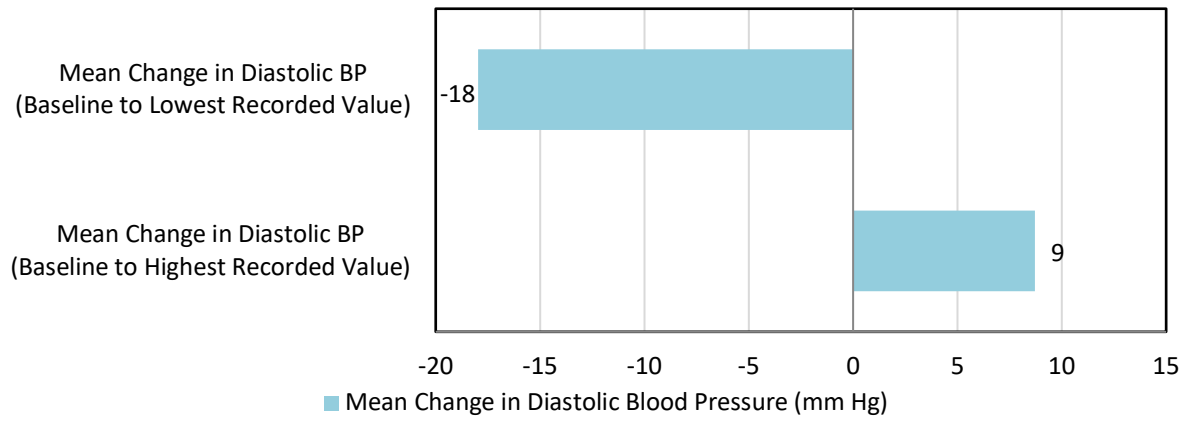
According to the AHA (2021b) and the CDC (2021), normal systolic and diastolic BP are less than 120 mm Hg and 80 mm Hg, respectively. Approximately 60% of the patient sample had elevated systolic BP according to the AHA (2021b) and CDC (2021) guidelines. Mean systolic BP was 128 mm Hg (Figure 6). During ANR, mean lower and upper boundary (i.e., mean maximum and minimum values from baseline) were 103 mm Hg and 139 mm Hg, respectively. Although BP transiently increased during the ANR procedure, this may be attributable to induction of opioid withdrawal which reflects the physiological symptomology response that is associated with a release of catecholamines (Shah & Huecker, 2023).

Figure 3. *Mean Change in Systolic BP During ANR.*



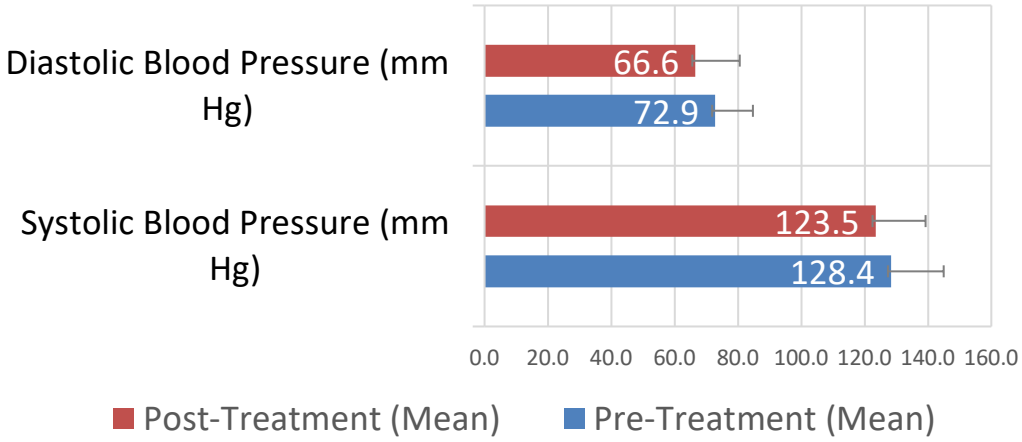
Note. ANR = accelerated neuroregulation; BP = blood pressure; mm Hg = millimeters of mercury.

Figure 4. *Mean Change in Diastolic BP During ANR Procedure.*



Note. ANR = accelerated neuroregulation; BP = blood pressure; mm Hg = millimeters of mercury.

Figure 5. *Mean BP Normalizes After ANR Procedure.*

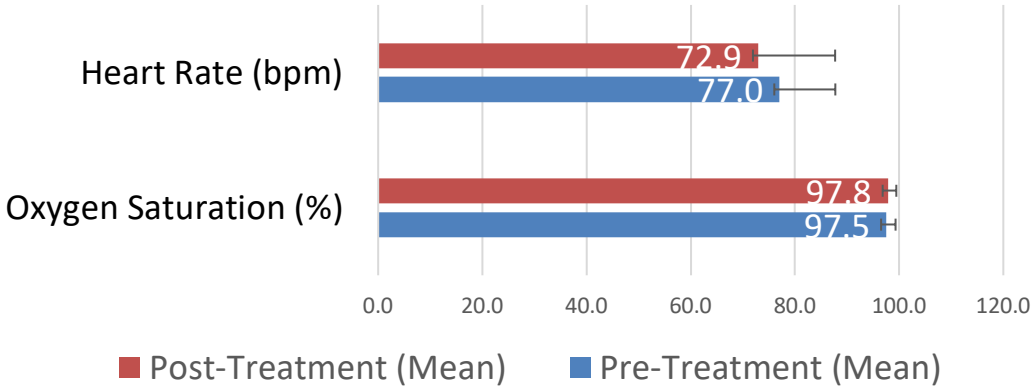


Note. ANR = accelerated neuroregulation; BP = blood pressure; mm Hg = millimeters of mercury.

Oxygen Saturation During ANR Procedure

Highest and lowest oxygen saturation values were recorded during ANR procedures and reviewed for this analysis. These values were then normalized from baseline (i.e., subtracted from each highest and lowest recorded value) and averaged, respectively, across the patient sample. Average lower and upper boundary oxygen saturation levels during treatment were 96.8% and 99.1%, respectively. From pre- to post-ANR procedure, mean oxygen saturation changed approximately 0.3% (Figure 6). As normal physiological oxygen saturation at sea level is between 96% and 99%, this suggests minimal fluctuation during ANR procedure (Shaikh, 2022). No adverse events related to oxygen saturation (i.e., hypoxia or difficulty breathing) were reported during treatment for this sample of patients. As a result, patients demonstrated pulmonary stability during and after ANR procedure.

Figure 6. *Mean Heart Rate and Oxygen Saturation Pre- and Post-ANR Procedure.*



Note. ANR = accelerated neuroregulation; BP = blood pressure.

Conclusion

Results showed no significant variability in cardiovascular or hemodynamic data during any interval of ANR procedure (i.e., intra- or posttreatment). Additionally, no adverse events related to oxygen saturation (i.e., hypoxia or difficulty breathing) were seen during any interval of ANR procedure for this subset of patients. As a result, patients who underwent the ANR procedures demonstrated hemodynamic and pulmonary stability during and after ANR treatment. This preliminary evidence shows that the ANR procedure is a safe and effective procedure with low risks resulting from a structured, evidenced-based protocol and treatment plan.

Advantages of ANR Treatment

Induced withdrawal as a result of ANR procedures reduces the adverse withdrawal symptomology. Non-ANR treatments (rapid detoxification) typically do not rebalance or return opioid receptors back to their original status and result in adverse symptomology and long-term effects for the patient. As a result, patients undergoing these treatments still have cravings and are at increased risk for relapse. The ANR procedure achieves the therapeutic goal of rebalancing the entire endorphin receptor system while providing a safe intervention with few adverse effects.

Author Disclosure

We have no known conflict of interest to disclose.

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