Revolutionizing Management of Sleep Disorders: The Utility of ORP for Clinical Sleep Medicine

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The Problem

There is room in the field of sleep medicine for novel metrics to assess sleep disorders and allow for a more personalized approach to sleep disorder management. For instance, the apnea-hypopnea index (AHI) has been recently criticized because it doesn't always associate with clinical symptoms, particularly measures of daytime sleepiness[1], and is poor in determining who most needs treatment and the type of treatment most appropriate[2]. There is a push to find other measures that can provide additional clinical information with greater utility.

Other aspects of sleep are measured by extracting the sleep stages from the standard polysomnogram (PSG); however, this method reduces a vast amount of physiological data down into several summary measures. Additionally, standard sleep staging has some weaknesses due to the use of arbitrary definitions to distinguish different stages[3]. These definitions based on arbitrary cut-offs allow the classification of different patterns of brain activity in the same stage, and of very similar patterns into different stages. Above all, the summary of sleep into different stages leaves aspects of brain activity unmeasured, which could have diagnostic consequences (see Figure 1).

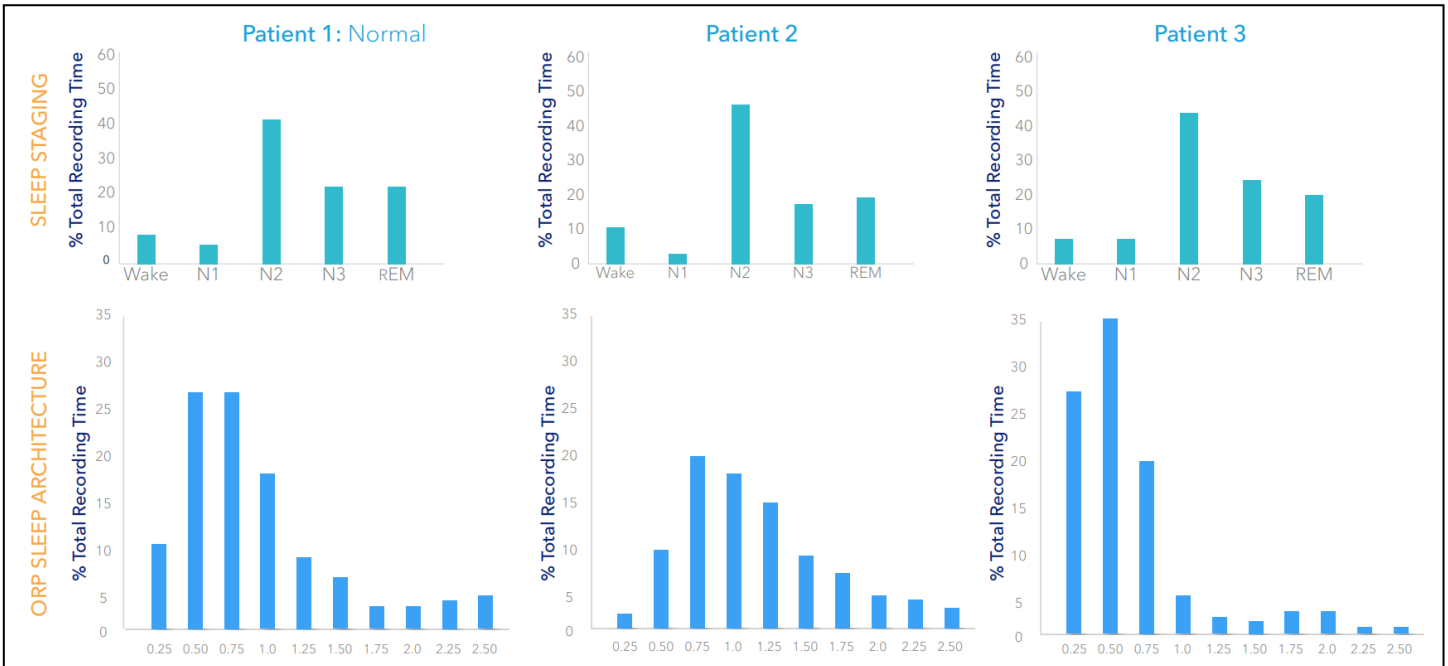

Figure 1. For the three patients above, their conventional sleep architecture across the top row is normal and similar. However, when looking at their sleep patterns using ORP Sleep Architecture, it reveals very different patterns of sleep quality across the night. Subject 1 displays a normal ORP architecture, with balanced time spent in both deep sleep and in full wakefulness. Subject 2 is lacking deep sleep, suggesting a disruption to sleep (e.g., sleep apnea) which prevents them from reaching the deepest sleep; at the same time low time spent in full wakefulness suggests that they are not meeting their sleep need. Subject 3 is lacking full wakefulness and has excessive deep sleep, which suggests a state of sleep deprivation and a need for more sleep. These differences would never have been revealed with conventional sleep staging.

Tackling these challenges of measurement and definition could lead to improvements in the management of sleep disorders. For instance, adherence to CPAP is low, ranging from 30-60% across studies, even when using lenient criteria of 4 hours of use per night for 70% of nights[4]. There is thus a hunt in the field to find methods to help increase adherence. Also, physiological markers of insomnia that would justify using polysomnography (PSG) for diagnosis have remained largely elusive, leaving only subjective complaints as criteria. There are often no differences in standard polysomnographic variables between controls and patients with insomnia with short sleep duration, who make up approximately 40% of all insomnia sufferers[5,6]. This is due to a lack of sensitivity of traditional metrics to distinguish factors differentiating sleep in patients with insomnia.

The Solution: Odds ratio product (ORP)

"Conventional sleep scoring methods don't capture the true depth of sleep. The holy grail of sleep research is a metric of sleep depth. That's a major move forward in medicine and health care."
– Dr. Charles Samuels

The Odds ratio product (ORP) was invented to target some of the challenges that are present with standard sleep staging, further the development of novel diagnostic strategies, and assist in the creation of personalized treatment plans based on an individual's needs. ORP is a highly validated measure of sleep depth[3] ranging from 0 (deep sleep) to 2.5 (full wakefulness) (See Figure 2).

Based on the EEG power in different frequency bands across the recording, which are then compared to historical sleep study data, ORP determines the probability of a certain epoch of being scored awake or asleep providing a measure of sleep depth every 3 seconds across the night. By examining the EEG power across several frequency bands (alpha, beta, theta and delta), ORP better uses the wealth of data that is collected from the PSG about the states of the brain during the sleep period. It has gained validity as a sensitive marker of objective sleep depth[3,7]. When presented alongside the standard sleep staging, ORP can be a powerful tool that provides valuable additional information on the patient's sleep depth and quality.

ORP can be presented in different ways, each providing a novel way to characterize sleep and markers of poor sleep. First, ORP can be presented as a numerical value during each stage

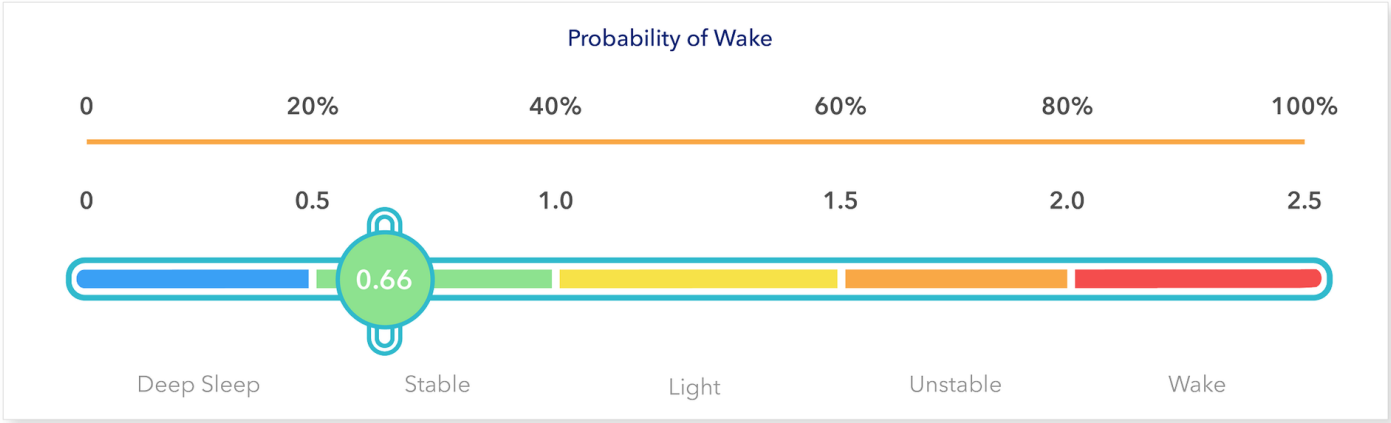

Figure 2. The range of values in ORP of 0 (deep sleep) to 2.5 (full wakefulness) with light, transitional sleep occurring in the middle of the scale.

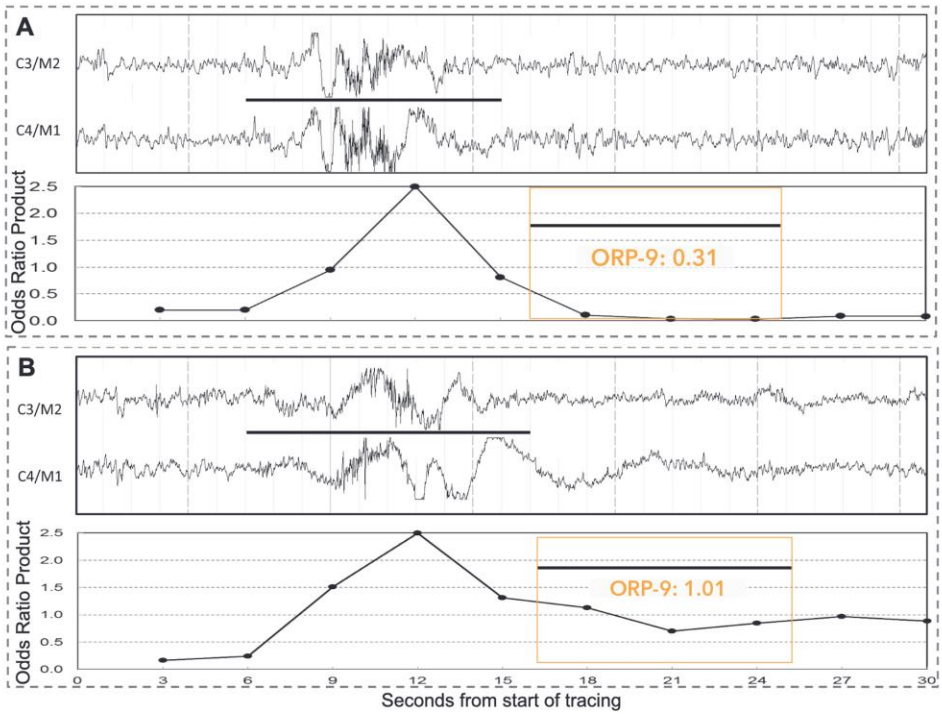

Figure 3. In this figure, the period where ORP-9 is measured is depicted by the black bar at the end of the arousal in the orange rectangle. As can be seen, patient A has a very low ORP after the arousal, and immediately descends to quite low levels of ORP. However, in patient B, after the arousal, the ORP remains elevated, with shallower sleep depth and higher chances to be woken up by further arousals leading to poor sleep quality.

of sleep during the night, and during the total recording. Next, ORP-9 can be extracted, which reports the average ORP across 9 seconds after an arousal[8]. It reflects the sensitivity of an individual to disruptions in their sleep and the ability to recover from an arousal. It is currently believed to be a trait measure that is determined by a central system and is not due to excessive arousal stimuli or the presence of sleep disorders, such as sleep apnea or periodic limb movements[7]. An example of different levels of ORP-9 can be seen in Figure 3.

Recent work has developed a new method for visualizing the percentage of time spent at different levels of the ORP scale, which we call ORP architecture. ORP architecture graphically depicts ORP across the total recording at each of ten different depths of ORP (see Figure 4). The overall capture of these different patterns is assigned a two-digit number, reflecting the percentage of time that a patient is in deep sleep (the first two deciles) or full wakefulness (last decile)[9]. Patients can fall into low (<25th percentile), average (25-75th percentile), or high (>75th percentile) values of deep sleep or full wakefulness generating 9 potential patterns. Recent research has proposed physiological mechanisms, and potential interpretations to stimulate future research questions on these patterns (see Figure 4).

"Optimal patient care in Sleep Medicine requires a better understanding and measurement of sleep. One such dimension is sleep depth, and Odds Ratio Product provides important and unique information directly applicable to patient management, including sleep apnea, insomnia, and hypersomnia."
– Dr. Robert Thomas

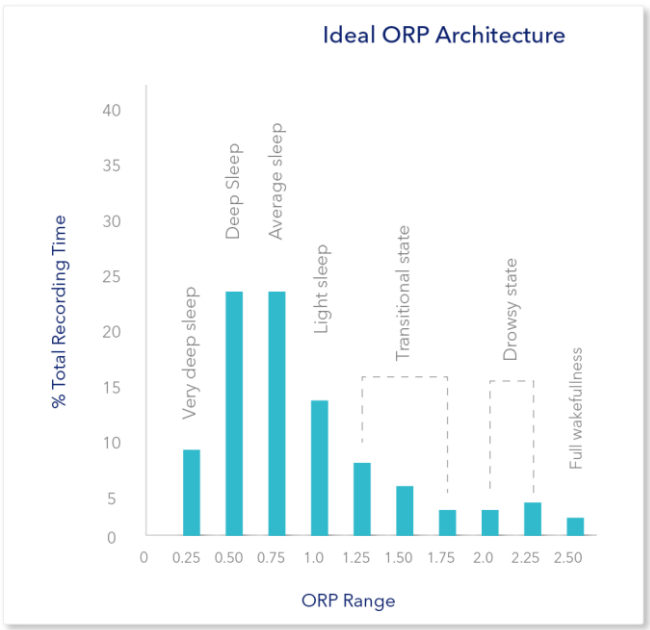

Figure 4. This figure illustrates an example of "ideal" ORP architecture, where there is plenty of very deep and deep sleep, but full wakefulness is additionally represented.

How can ORP help in the diagnosis of insomnia?

When comparing ORP metrics in patients with insomnia and patients with no sleep disorders, ORP measured during wake periods of the recording (ORP_{wake}) is elevated[10]. This result supports the hyperarousal model of insomnia, which argues that increased biological and psychological arousal can be a driver of the development of insomnia[11]. Consistent with typical presentations of insomnia, higher ORP_{wake} has also been associated with lower reports of daytime sleepiness[12]. High ORP measured during NREM (ORP_{NREM}) has also been found in patients with insomnia, reflecting lighter sleep[10]. High ORP_{NREM} has been associated with worse reports of subjective sleep quality, which supports the interpretation of light and poor quality sleep[12]. Finally, patients with insomnia had higher ORP-9, reflective of sleep more sensitive to disturbances.

ORP architecture has indicated differences between patients presenting with insomnia with short sleep duration and individuals with no sleep disorders. In these patients, patterns 1,3 and 2,3 (see Figure 5), were the most dominant[9]. Specifically, these patterns are associated with low or average deep sleep and excessive time spent in full wakefulness. While these patterns are often seen in an aging population, their presence in a patient might be an indicator of insomnia with high amounts of full wakefulness suggesting low sleep pressure, as the patient is not remaining drowsy during nighttime wake periods.

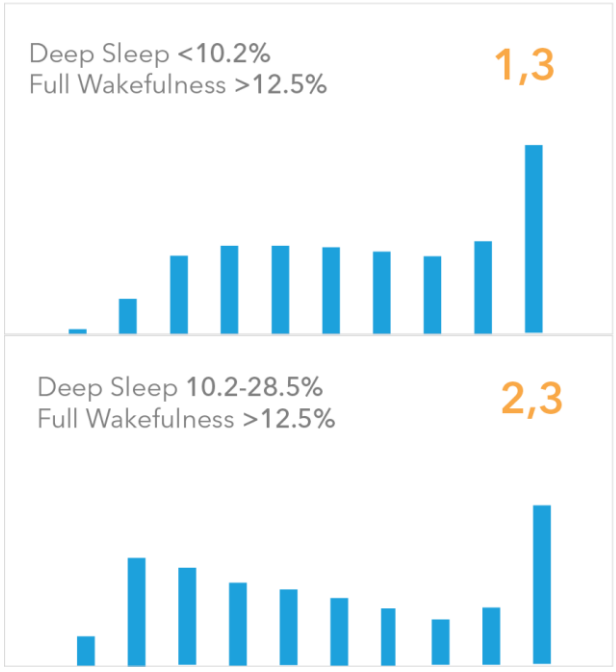

Figure 5. ORP architecture types 1,3 and 2,3, the two main patterns associated with insomnia with short sleep duration[9].

Future research will need to determine if patients with insomnia who also have low amounts of deep sleep (type 1,3), are the patients most at risk of the negative health outcomes often associated with insomnia, such as hypertension, diabetes, and cognitive decline[13]. More research is also needed to identify potential markers of insomnia with normal sleep duration, and to assess how ORP responds to treatment for insomnia. However, the research conducted so far has held initial promise for ORP as a diagnostic marker of hyperarousal due to insomnia, alongside with

patient complaints. It is hoped that further research, ORP will be useful in diagnosing insomnia and informing the most appropriate treatment pathways.

How can ORP assist in diagnosis and development of treatment plans for obstructive sleep apnea?

ORP can shed some light on why patients might be differentially affected by severe respiratory events. Patients with OSA typically have a higher ORP-9 than patients with no sleep disorders[10]. A high ORP-9 can be a mechanism of sleep disruption, where excessive arousal stimuli, like respiratory events, can prevent the patient from obtaining any sleep at a restorative depth[8]. When an arousal occurs, a patient with a high ORP-9 remains in a state of light sleep for longer, where they are susceptible to more arousals. On the opposite side, a low ORP-9 can provide some protection with less vulnerability to arousals. Despite large changes in AHI after initiation of CPAP, ORP-9 does not seem to change with CPAP usage, which supports the idea of its trait-like nature[8]. A reduction in the number of arousing stimuli, from either CPAP treatment, or from modifying the external environment are necessary to allow a patient to get better sleep.

Patients with OSA have higher ORP_{NREM} than individuals with no sleep disorders, which reflects the disruption to their sleep from repeated respiratory events[10]. They also have lower ORP_{wake} than no sleep disorders, distinguishing them from patients with insomnia. A lower ORP_{wake} is consistent with reports of excessive sleepiness seen in patients with sleep apnea[14]. In terms of ORP architecture, the number of patients presenting with patterns 1,1, 1,2, and 1,3 increases with severity of sleep apnea[9] (see Figure 6). Specifically, in very severe sleep apnea, nearly 62% of patients presented with one of these patterns with a much greater prevalence than in patients with no sleep disorders. These types are characterized by low amounts of deep sleep, likely due to the presence of respiratory events preventing deep sleep, but also low amounts of full wakefulness, reflecting the drowsiness and high drive for sleep.

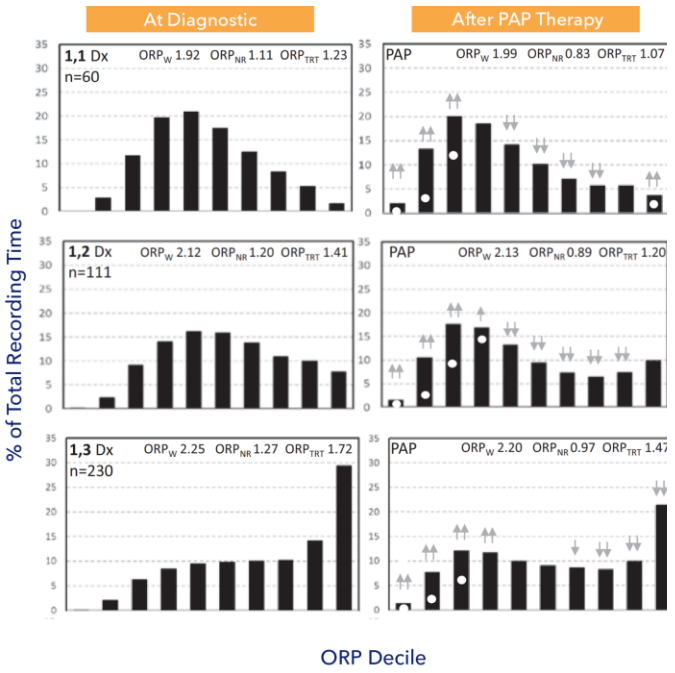

Figure 6. The three OSA ORP architecture types at diagnostic (left image), and after PAP therapy (right image)[15]. These patterns show improvement with treatment, in that more time is spent in deep sleep and less time is spent in unstable levels of sleep depth.

Similarly, these same types are also the ones that respond well to treatment with CPAP with improvements in sleep depth (see Figure 6)[15]. In a recent study pre-post CPAP treatment, time spent in deep sleep increased post treatment, with a concomitant increase in full wakefulness for the patients presenting with the 1,1-type, indicative of greater satiation and less pressure for sleep. The other architecture types did not show the same degree of improvement or had worse sleep after CPAP. Importantly, these results show the possibility to predict response to treatment following the diagnostic sleep study, with patients presenting with these three types being ideal candidates for CPAP.

Actual adherence to PAP therapy is an important issue in the field of clinical sleep medicine, with over 3700 articles mentioning "improving adherence in CPAP users" from 2018 to 2022 (dimensions.ai). Ensuring adequate treatment of OSA is important to reduce comorbidities and cardiovascular risk[16], however, attempts to increase adherence in practice have not been overly successful.

Recent research has shown that PAP adherence at the one-year mark can be predicted using a model derived from variables measured during the diagnostic sleep study, which generate an "Adherence Index". The adherence index is calculated using ORP_{NREM}, mean SpO_2, and AHI from the diagnostic study[17] (see Figure 7). High ORP_{NREM}, reflective of poor sleep quality, combined with high AHI, reflecting greater respiratory events, and a lower mean SpO_2, are associated with greater likelihood of improved sleep post PAP, and consequently, better predicted adherence. For patients with lower ORP_{NREM}, and better sleep quality, the perceived benefits to their sleep with CPAP may not be sufficient to counter the somewhat disruptive nature of the PAP equipment, as users often complain of inconvenience, claustrophobia, and discomfort[18]. Patients predicted to have low adherence may be patients that are good candidates for other treatment options, or who need additional support to achieve good adherence rates. It is hoped that knowledge at diagnosis of whether a patient is likely to be adherent to PAP therapy, will provide an opportunity for early intervention to promote better adherence in these patients.

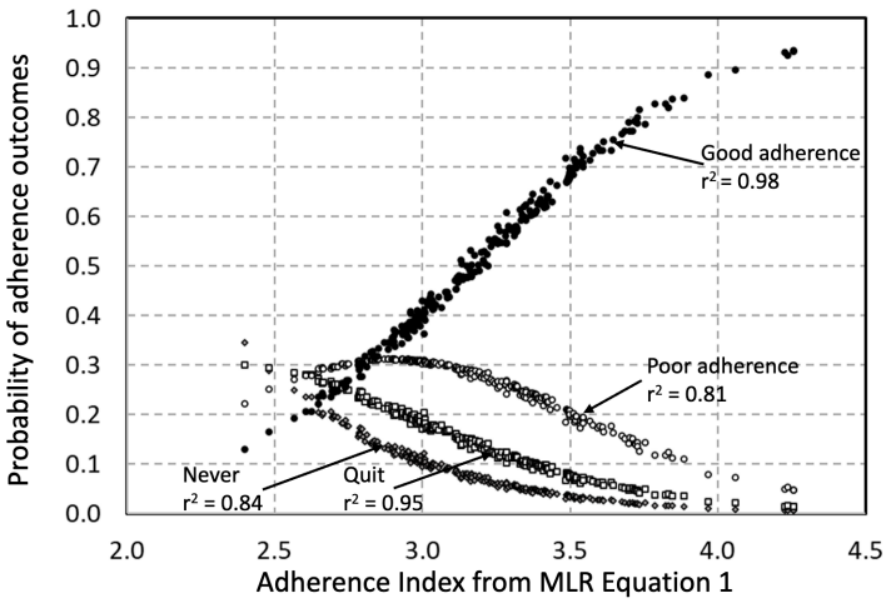

Figure 7. The Adherence Index calculated from the diagnostic sleep study and the probability of good adherence. As the Adherence Index increases, so does the probability of good adherence which supports the validity of the index[17].

Discussion and Future Directions

Further research is being undertaken to fully explore the diagnostic utility of ORP. Cerebra has a unique research opportunity through the contract with the Manitoba government to help alleviate the diagnostic sleep study backlog. With access to such a large pool of patients with sleep complaints, the clinical utility of ORP will be assessed. Overall, this study will target whether there is a physician-perceived benefit to having access to ORP information. This aim will be completed by comparing diagnostic confidence and treatment outcomes when ORP is provided to when it is not provided (see Figure 8 for full study design). It is expected that this study will shine a light on the value of ORP for sleep medicine physicians.

Following the investigation of the main aim of the study, we will further examine the impact of ORP in the evaluation and treatment of specific sleep disorders in different research arms. For OSA, the Adherence Index will be further validated by comparing the agreement between predicted adherence and actual adherence at 12 months. For insomnia, ORP will continue to be investigated as a potential diagnostic marker with the goal to better understand which sleep diagnostic markers are most predictive of good treatment outcomes. Of particular interest will be research on COMISA. COMISA is a currently undertreated sleep disorder characterized by the comorbid diagnoses of insomnia and OSA[18]. ORP has begun to be investigated in this group, with findings of elevated ORP_{NREM} and ORP-9 compared to individuals with no sleep disorders[10]. This initial project will assess predictors of good treatment outcomes in COMISA patients. After the initial studies, for each treatment arm, further intervention studies are planned, where efforts will be made to increase adherence to treatment and inform which treatments have the greatest positive impact on ORP and patient outcomes. Other datasets are also exploring the potential role of ORP in other sleep disorders, such as hypersomnia.

There is a drive in the field of sleep medicine to determine better and more specific diagnostic markers. ORP stands as a prime candidate to provide additional insight into the impact of a sleep disorder on a patient's sleep allowing for a more personalized approach to diagnosis and treatment.

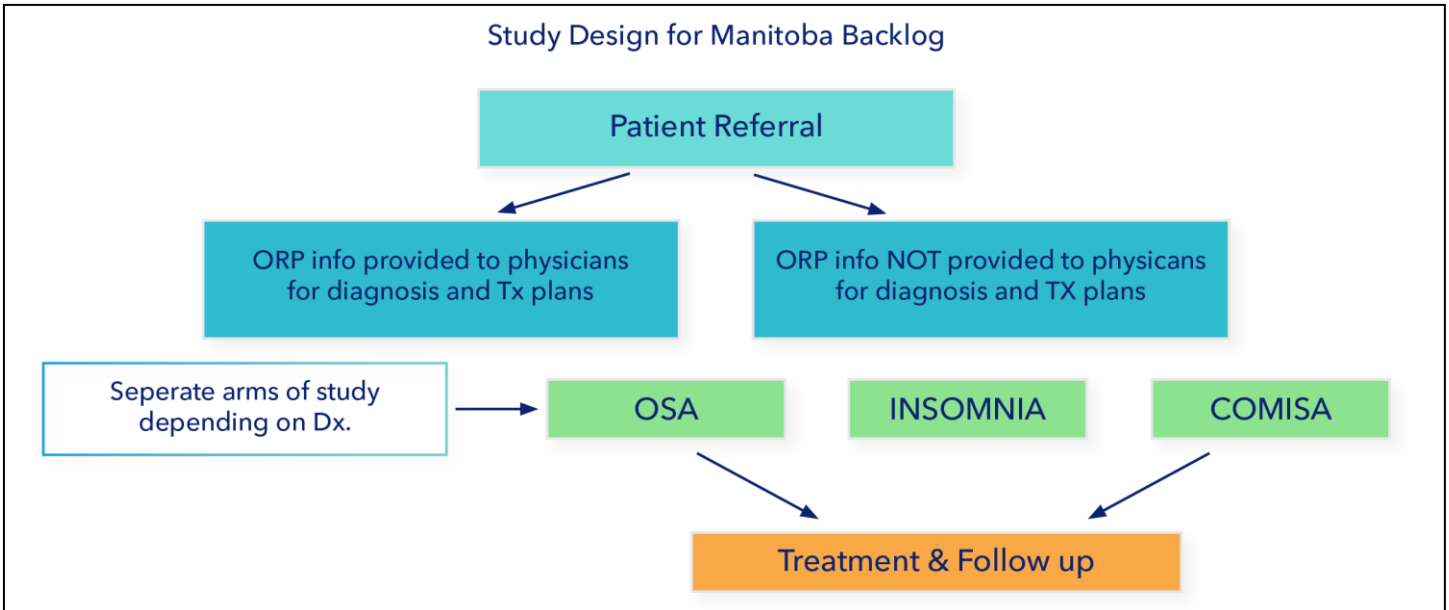

Figure 8. Proposed study design for Manitoba Backlog study. Physicians may or may not receive ORP information for each patient, and the benefit of receiving ORP information can be assessed.

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