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International Publication Milestone for BAR Monitor

Cortical Dynamics Limited, an investee company of BioPharmica is developing a unique depth of anesthesia monitoring system for use during major surgery. The core technology is based on real time analysis of the patients electroencephalogram (EEG) using a proprietary algorithm based on a mathematically and physiologically detailed understanding of the brain's rhythmic electrical activity. The theory developed by Professor David Liley, who heads the scientific team at Cortical Dynamics, for the first time provides a meaningful way of relating brain electrical activity to the underlying physiological processes that generate it. Cortical Dynamics is confident that the resulting BAR (Brain Anesthesia Response) analysis methodology and index will be a more sensitive measure of the state of the brain during anesthesia than the current alternatives, all of which are based on detecting empirical correlations between subjective assessments of the level of consciousness and a range of parameters derived from the quantitative analysis of EEG.

Two clinical trials, utilizing the BAR methodology, have been completed at the Royal Melbourne Hospital. These trials were designed to evaluate the BAR technology in the presence of agents that affect the level of anesthesia which are known to be problematic to monitor using existing technology. To date the results of both sets of trials have provided support for the increased sensitivity of the BAR algorithm enabling enhanced detection of anesthetic drug effect.

The detailed results of one of these trials have now been published in the peer reviewed international journal *Computers in Biology and Medicine*, thereby providing scientific acceptance for the BAR analysis methodology. The paper entitled "Dissociating the effects of nitrous oxide on brain electrical activity using fixed order time series modeling" *doi: 10.1016 / j.compbiomed.2008.08.011 (made available on-line from 2nd October 2008)* by David T.J. Liley, Kate Leslie, Nicholas C Sinclair and Martin Feckie reports the significant results of a trial conducted to compare the sensitivity of the BAR algorithm to the market leading BIS Monitor (Aspect Medical Systems) in detecting the effects varying levels of adjuvant nitrous oxide had on measures of anesthesia induced by the common inhaled agent sevoflurane.

The abstract states:

"A number of commonly used anesthetics, including nitrous oxide (N_2O), are poorly detected by current electroencephalography (EEG)-based measures of anesthetic depth such as the bispectral index. Based on a previously elaborated theory of electrocortical rhythmogenesis we developed a physiologically-inspired method of EEG analysis that was hypothesized to be more sensitive in detecting and

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characterising N_2O effect than the bispectral index, through its combined EEG estimates of cortical input and cortical state. By evaluating sevoflurane-induced loss of consciousness in the presence of low brain concentrations of N_2O in thirty eight elective surgical patients, N_2O was associated with a statistically significant reduction in the input the frontal cortex received from other cortical and subcortical areas. In contrast the bispectral index responded only to low, but not to high, concentrations of N_2O."

In the context of these results Professor David Liley commented that "The acceptance for publication of the nitrous oxide trial results represents a major milestone in the BAR project as it signifies that the fundamental algorithmic approach is deemed to be valid and useful. Significantly, such peer acceptance, means that we are now able to complete the analysis of EEG trial data involving the administration of opioids and other agents where we also anticipate superiority over existing monitoring approaches"

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