

## A double-blind placebo-controlled crossover study of phenytoin in individuals with impulsive aggression

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### Abstract

The present study examines the behavioral and psychophysiological effects of phenytoin (PHT) in individuals who display impulsive-aggressive outbursts. In a double-blind placebo-controlled crossover design, individuals meeting previously established criteria for impulsive aggression were administered PHT and placebo during separate 6-week conditions. The efficacy measures used were the Overt Aggression Scale (OAS) and the Profile of Mood States (POMS). Psychophysiological measures (evoked potentials) were taken at baseline and at the end of each 6-week condition. Photic stimulation was used to evoke the mid-latency P1–N1–P2 waveform complex. Analysis indicated a significant decrease in the frequency of impulsive-aggressive outbursts during PHT administration compared to baseline and placebo. Analysis of the psychophysiological data showed significantly increased P1 amplitude and significantly longer N1 latency during PHT administration. In addition, a reduction in N1 amplitude during PHT administration was also suggested. These findings indicate reparation of physiological abnormalities previously observed in impulsive-aggressive individuals and imply more efficient sensory processing and effective orienting of attention. Taken together, these results provide insight as to the physiological mechanisms by which PHT serves to ameliorate impulsive-aggressive behavior. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

*Keywords:* Aggression; Phenytoin; Evoked potentials; P1; N1

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## 1. Introduction

Within the research literature, aggressive behavior has traditionally been classified into two distinct subtypes (Feshbach, 1964; Dodge and Coie, 1987; Vitiello et al., 1990; Barratt, 1991; Barratt et al., 1997b, 1999): (1) an emotionally charged, uncontrolled type of aggressive display (impulsive, unintentional, affective, reactive) or (2) a planned, controlled, unemotional aggressive act (premeditated, intentional, predatory, proactive). Research suggests that this first subtype, impulsive aggression, may have biological underpinnings related to deficits in physiological arousal (Barratt et al., 1997a,b). Psychophysiological measures in these individuals have indicated a low level of arousal during resting conditions (Fishbein et al., 1989; Convit et al., 1991; Barratt et al., 1997b; Mathias and Stanford, 1999). It has been hypothesized that this low arousal leads to sensation-seeking and impulsive behaviors as well as a reduction in the efficiency of executive functioning (Eysenck and Eysenck, 1985, p. 249). In addition, impulsive-aggressive individuals show greater physiological reactivity as compared to controls (Mathias and Stanford, 1997). It has been suggested that sudden surges in arousal induce an agitated state that the impulsive-aggressive individual is unable to control.

Previous studies using evoked and event-related potential techniques have begun to shed some light on the psychophysiological substrates that underlie this problem behavior. Research utilizing photic stimulation has demonstrated an increase in P1-N1 amplitude in response to increasing stimulus intensity (augmenting) in impulsive-aggressive subjects (Houston and Stanford, 2001). In conjunction with this increased augmenting, P1 amplitude is smaller, N1 amplitude is generally larger and P1-N1-P2 latency is shorter in impulsive aggressors (Houston and Stanford, 2001). Specifically, the reduced P1 amplitude exhibited in this sample is hypothesized to reflect a deficiency in sensory gating (Rosenstein et al., 1994; Houston and Stanford, 2001). This deficit is further reflected in the greater physiological reactivity that characterizes impulsive-aggressive individuals (Barratt, 1963; Mathias and Stanford,

1997). Furthermore, inefficient sensory gating may also contribute to the deficient cognitive processing seen in impulsive-aggressive individuals during event-related potential paradigms (i.e. P3; Barratt et al., 1997b; Mathias and Stanford, 1999). The N1 amplitude, usually thought to indicate orienting or attention, has also provided insight into the physiological aberrations demonstrated in impulsive-aggressive samples. The larger N1 amplitude in these individuals indicates a different response to evoking stimuli. This response is thought to be indicative of the impulse aggressor's constant search for stimulation in an effort to boost arousal to a more optimal level. In addition, the shorter evoked potential (EP) latencies demonstrated by impulsive-aggressive individuals are also thought to reflect this constant search for stimulation. Furthermore, larger N1 amplitudes in response to increasing stimulus intensities, as compared to controls, lend support to the notion of greater physiological reactivity in this sample. Taken together, these psychophysiological results provide further evidence of arousal modulation deficits underlying impulsive-aggressive behavior.

In light of previous research indicating psychophysiological irregularities in impulsive aggression as well as clinical treatment of such behavior, the efficacy of various pharmacological agents has been investigated. One medication that has shown ameliorative effects specific to impulsive-aggressive behavior is the anticonvulsant phenytoin (PHT; Dilantin<sup>®</sup>, Parke-Davis). In normal subjects, administration of phenytoin results in prolonged EP latencies (P1, N1) and a reduction in N1 amplitude (Barratt et al., 1986; Yagyu et al., 1991; Akaho, 1996). These effects are contrary to those EP abnormalities (shorter P1-N1-P2 latency, higher N1 amplitude) exhibited by impulsive-aggressive subjects (Houston and Stanford, 2001). Psychiatric patients with episodic dyscontrol syndrome showed significant reductions in violent outbursts during treatment with phenytoin (Maletzky, 1973; Maletzky and Klotter, 1974). Similarly, incarcerated inmates whose aggressive behavior was classified as impulsive in nature showed significant reductions in the frequency and intensity of aggressive acts, normalization of event-related potentials (P3), and improvement in

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