Reviewer's report

Title: Auditory target processing in methadone substituted opiate addicts. The effect of nicotine in controls.

Version: 1 Date: 19 June 2007

Reviewer: Brian O'donnell

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Given the prevalence of opiate use, there are surprisingly few studies of brain electrophysiology in opiate users or former users in the literature. In the current study, the auditory P300 response was compared in methadone treated opiate dependent individuals and control subjects. No differences were found between groups for P300 amplitude or latency, suggesting that methadone treatment has little effect on this component. In addition, P300 amplitude was compared between control subjects who did and did not smoke. Nicotine users showed reduced P300 amplitude compared to non-users.

Strengths: The lack of P300 differences in methadone users is an important negative finding. There are many studies suggesting that genetic risk and personality characteristics associated with alcohol or substance use are associated with reduced P300 amplitude, but it is unclear whether this is true of opiate users. The current study suggests this is not the case. The effect of nicotine use on P300 amplitude in control subjects is consistent with a number of studies demonstrating this relationship, and may indicate a more direct association between the nicotinic cholinergic system and P300 generation compared to opiate receptors.

An interpretative problem in the study is the heterogeneity of the methadone group. The duration of opiate dependency prior to methadone substitution, the duration of methadone use, and the dosage of methadone varies greatly among subjects. It is recommended that these variables be tested for correlation with P300 measures. The majority of methadone users use other psychoactive drugs. All methadone users used nicotine.

If nicotine use is associated with P300 amplitude reduction, then it is puzzling why the methadone users, who all use nicotine, do not show amplitude reduction. This suggests some sort of pharmacological interaction between methadone use and nicotine use, and this issue should be addressed in the discussion. It would be worthwhile to investigate this issue more systematically not the statistical analyses.

The description of the statistical analyses is sometimes vague. For example, the statement, “The same analysis within subgroups...” does not specify which subgroup comparison is being tested. This analysis reveals a main effect of group but no group X electrode interaction. It is therefore unclear why group...
effects were, “...further evaluated in group X electrode follow-up analyses,” which would only be necessary if there was an interaction. F values and degrees of freedom should be provided as well as p values.

The Kouri et al (1996) paper does not seem to be accurately represented in the discussion. Kouri et al (1996) found no differences between opiate users, but reduced P300 after detoxification. The subjects in the present study are more comparable to current opiate users than with detoxified non-users, since methadone also is an opiate agonist. The current results therefore seem consistent with Kouri et al, since use of opiate agonists appears to be associated with minimal changes in P300.

The discussion could be shortened.