Smoking and sub-therapeutic fluvoxamine serum levels: Are epigenetics to blame?

Kristen N. Gardner, Amanda N. King, Rachel E. Rarus, Janis M. Rood

Department of Clinical, Social and Administrative Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI USA

INTRODUCTION

Cigarette smoking and dependence are associated with psychiatric disorders, notably depression, which affects nearly 10% of the U.S. population. The chemicals present in cigarette smoke have been shown to induce the expression of cytochrome P-450 (CYP) enzymes, and as such, the metabolic effects of smoking warrant consideration in the context of pharmacotherapy. Specifically, in smokers compared to non-smokers, studies have shown lower serum levels of fluvoxamine, which is extensively metabolized by CYP2D6. Elucidation of the biochemical mechanism underlying decreased serum levels is critical, given the increasingly relevant debate on personalized medicine. Previously, research has shown increased acetylation of histone 3 and 4 in rat lungs exposed to cigarette smoke. However, alterations in epigenetic modifications such as histone acetylation, have yet to be investigated in the context of *CYP2D6* expression.

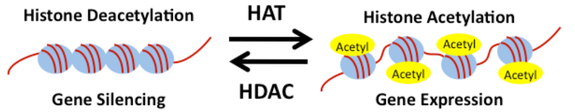


Figure 1. A schematic illustrating the effect of acetylation and deacetylation on chromatin remodeling and gene transcription.

HYPOTHESIS

Compared to non-smokers, current smokers will have decreased fluvoxamine serum levels, increased expression of *CYP2D6*, and increased histone acetylation.

SPECIFIC AIMS

1. Assess steady state fluvoxamine serum levels in current smokers and non-smokers.
2. Correlate steady state fluvoxamine serum levels with *CYP2D6* expression from acquired peripheral blood mononuclear cells (PBMC) in current smokers and non-smokers.
3. Compare histone acetylation status of DNA from acquired PBMC in smokers and nonsmokers.

METHODS

This will be a prospective, open-labeled study with n=220 subjects.

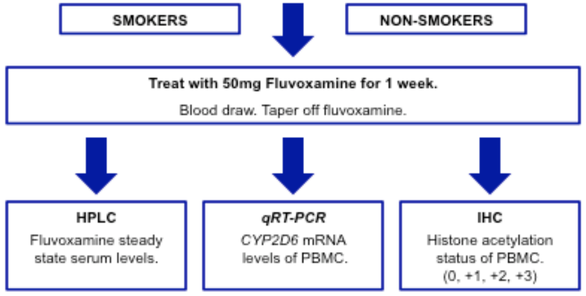
Inclusion Criteria

- Ages 25-65 years old.
- Healthy patient defined as absence of disease or presence of a controlled medical condition (other than nicotine dependence).
- Current smokers defined by a pack history ≥ 10 years or having achieved smoking cessation status for ≤ 3 months following a ≥ 10 pack year history.
- Non-smoker defined as never smoked or achieved cessation for ≥ 10 years.

Exclusion Criteria

- History of hepatic failure.
- Past or current alcohol dependence/addiction.
- History of seizure disorders.
- Women who are pregnant, planning to become pregnant, or currently breastfeeding.
- Receiving treatment with a pharmacological product that substantially alters CYP2D6 mediated metabolism.

STUDY DESIGN



DATA ANALYSIS

- Descriptive statistics will compare smokers to non-smokers using χ^2 analysis to assess differences in gender and race while an unpaired two-sided t-test with unequal variances will compare age.
- An unpaired two-sided t-test will be used to assess mean steady-state fluvoxamine serum levels (adjusted for age, gender, and co-morbidities) in smokers and non-smokers.
- A multivariate linear regression model, using age, gender, race and body weight as covariates, will be used to correlate fluvoxamine serum levels and *CYP2D6* relative expression levels of both smokers and non-smokers.
- The mean *CYP2D6* mRNA levels will be compared between groups using a two-sided t-test.
- A χ^2 test will be used to compare histone acetylation status between smokers and non-smokers.
- A two-sided p-value ≤ 0.05 will be considered statistically significant for all clinical endpoints.

CONCLUSIONS

- Subjects who smoke will have a reduction in steady state fluvoxamine serum levels compared to non-smokers.
- Decreased fluvoxamine serum levels will be correlated with increased *CYP2D6* mRNA with smokers exhibiting a significantly higher mean expression.
- Histone acetylation will be significantly increased in smokers compared to non-smokers.
- This research emphasizes the need for clinicians to diligently monitor fluvoxamine treated patients who are smokers.

LIMITATIONS

- Histone acetylation of *CYP2D6* was not specifically assessed.
- Fluvoxamine metabolism by CYP2D6 could be capacity-limited in some subjects.
- *CYP2D6* polymorphisms will not be analyzed.

FUTURE DIRECTIONS

- Determine if histone acetylation alterations of *CYP2D6* are influenced by smoking duration.
- Investigate the histone acetylation status of *CYP2D6*.
- Examine the ability of cigarette smoke to mediate *CYP2D6* genotypic variation and the impact on fluvoxamine serum levels.
- Examine the influence of cigarette smoke on histone acetylase and deacetylase activity.