Modafinil for Alcohol Dependence: In Search of Solutions to an Epidemic

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Effect of Modafinil on Impulsivity and Relapse in Alcohol Dependent Patients: A Randomized, Placebo-Controlled Trial

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The Role of the Frontal Lobes in Inhibition/Disinhibition

Alcohol abuse and dependence are a leading cause of morbidity and mortality in the United States and worldwide.[1] The problem has been tackled on many fronts, and real answers remain elusive.

The psychosocial and psychological aspects of alcohol dependence treatment and recovery are beyond the scope of this article, although they are probably of fundamental importance. The role of impulsivity and its neurobiological underpinnings in the etiology and progression of alcoholism has become a new avenue of intense study.[2,3]

To understand the role that impulsivity might play in the genesis and progression of alcohol dependence, it is necessary to first understand the role of the human frontal lobes in the proper inhibition of impulses. Efficient functioning of the frontal lobes and their connection to more primitive subcortical structures is needed for proper inhibition of impulses.[4-6] The advent of the frontal lobes by evolutionary processes added to the brain the capacity for task completion -- a critical cognitive task needed for our ancestors to survive.[7,8]

Dramatic examples of the loss of frontal lobe function can be observed in acquired frontal lobe injury, in which patients become more disinhibited and highly impulsive -- typically the reason they are seen by the psychiatrist in the first place. In other words, the frontal lobes are our "evolutionary brakes." Developmental, genetic, or structural (acquired) frontal brain loss turns the disciplined person into the undisciplined, and the reliable person into the opposite.

Impulsive Behavior in Alcoholism

In the field of alcohol dependence research, the role of impulsive behavior is critical because observational data point to a significant correlation between impulsivity and drinking patterns.[3] From a clinical standpoint, it is intuitive to arrive at that correlation; that is, the impulsive individual who, after a disastrous day at the office, does not think twice before stopping at the first bar he sees to have 1, 2, or 3 drinks -- ending with a "heavy drinking day," to use research lingo.

From an investigational standpoint, correlation might not always equate to causality, and therefore understanding the relationship between impulsive behavior and the onset and progression of alcoholism is of paramount importance. In other words, which came first? At the same time that some researchers work on this answer, others have realized that independent of this question, there is a

subset of these patients for whom impulsive behavior (frontal lobe function within overall malfunctioning frontal-subcortical circuits) is intimately tied to morbid drinking behavior.

This suggests that appropriate control of impulses by the frontal lobes is of great importance, and the efficient fine-tuning of neurochemical systems within frontal structures is critical to the modulation of more primitive subcortical structures. To that extent, the monoamines, such as dopamine and their modulation of glutamate (the main excitatory neurotransmitter in the frontal lobes), are of key importance when thinking about and researching new interventions for the treatment of alcohol dependence.[9,10] Dysfunctional dopaminergic connections to prefrontal (frontal lobe) regions, for instance, have been linked to drinking behavior.[10]

Enter Modafinil

Modafinil [2-(diphenylmethyl)sulfinyl]acetamide] is currently US Food and Drug Administration-approved for the treatment of narcolepsy, shift-work sleep disorder, and excessive daytime sleepiness associated with obstructive sleep apnea. Its potential off-label use in traumatic brain injury, Parkinson disease, child and adult attention-deficit/hyperactivity disorder, myotonic dystrophy, bipolar depression, and schizophrenia has also been researched.[11] Its wake-promoting properties are thought to be related to prohistamine effects, as well as modulation of the hypocretin/orexin neuropeptide system in the hypothalamus.

Preclinical data point to some degree of selectivity for this compound for the dopamine receptor (D_1), dopamine transporter (DAT), and norepinephrine transporter (NET).[12] Given modafinil's effects on D_1 (mostly located in prefrontal areas) as well as its blockade of DAT (therefore increasing dopamine availability in the synapse) and NET (increasing norepinephrine tone), it has been hypothesized that the drug's resultant procognitive effects could have a positive impact on prefrontal cortical (frontal lobe) impulsivity measures. If that is the case, then it could in theory help to reduce or prevent alcohol intake that is related to impulsive behavior.

This was precisely the hypothesis put forth by Joos and colleagues in the current study. Their aim was therefore 2-fold: to measure impulsive behavior, in this case using the Stop-Signal Reaction-Time (SSRT) task and the delay discounting task (DDT), and to measure drinking patterns by using the percentage of abstinent (from alcohol) days (%AD) and percentage of heavy drinking days (%HDD).

Study Findings and Implications

With respect to primary outcome measures, the investigators found an overall increase in drinking behavior with a reduction in %AD, as well as an increase in %HDD. They found an overall improvement in impulsivity (SSRT task) in the modafinil group.

In subgroup analyses, the investigators further assessed whether impulsive behavior had a more direct effect on modafinil's effect on drinking behavior. After they divided the SSRT task into 2 groups (high vs low impulsivity) on the basis of the median split, they found that patients with higher initial impulsivity tended to experience slower declines in %AD, meaning that it took those patients more time to return to previous drinking patterns than the non-modafinil group and the initial low-impulsivity group.

Can Something Positive Be Gained From a Mostly Negative Study?

Although the main analysis in this study did not reveal a statistically significant effect of modafinil on drinking patterns, an analysis of specific subset of individuals with initial high impulsivity measures did. Nevertheless, a conclusion that modafinil has an effect on impulsive drinkers should not be made just yet. From a statistical perspective, the results of subgroup analyses are to be taken as exploratory -- which means as a preamble to something that might be significant on the one hand, or may end up not meaning much, clinically speaking.

With this in mind, there are multiple lines of preclinical and clinical evidence[13-15] that point to modafinil's potential in addictive disorders with impulsivity. With an illness that has become epidemic, an intervention with some potential for benefit in highly impulsive alcoholics is fair game, assuming there are no potentially severe adverse effects (which were absent in this study). Although mostly negative, this study showed hints of a possible significant effect of modafinil on drinking behavior, which may have been obscured by not being well powered (meaning that the sample wasn't large enough for the question being asked). Therefore, in terms of dictating the standard of care, these results should be taken with caution, and certainly a risk-to-benefit analysis should carefully be performed if modafinil is to be used off-label.

Take-Home Points for the Clinician: The Where and How

- Impulse control is dictated by healthy frontal lobe function;
- Impulsivity in alcoholics is hypothetically related to dysfunctional frontal lobe function;
- Modafinil, owing to its effects on D_1, DAT and NET, is purported to be selective to prefrontal areas;
- Preliminary results point to modafinil ability to reduce measures of impulsivity; and
- There is some evidence resulting from subgroup analyses that modafinil mighthave an effect on alcoholics with a tendency for impulsivity. This result is to be understood as exploratory, and therefore in this patient population, modafinil should be used with caution.

Abstract

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