I remember it well. It was Thanksgiving 2008, I had just finished my third helping of turkey and cranberry sauce. I was catching up on my reading of past issues of "Biological Psychiatry' (I was about a year behind.) At that moment I was finishing an interesting but inaptly **(Why?)** titled paper by my friend Suchitra about naltrexone and alcoholism. Always on the lookout for new ideas for imaging studies, I was excited to read the authors' speculations, below.

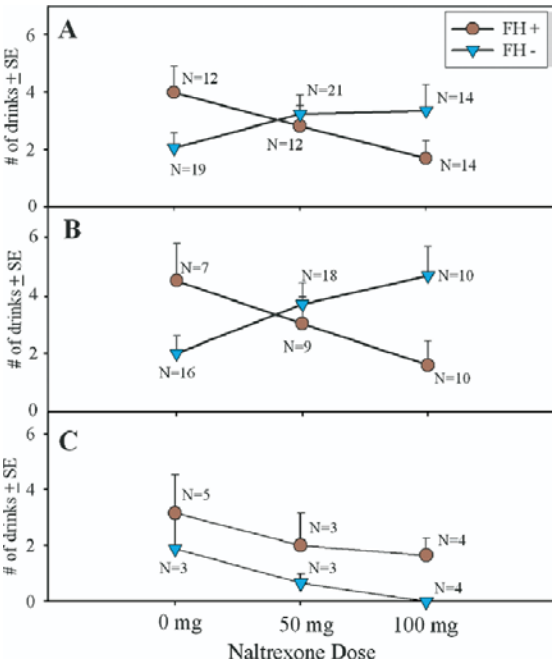
BIOL PSYCHIATRY 2007;62:694–697

Family History of Alcoholism Influences Naltrexone-Induced Reduction in Alcohol Drinking

Suchitra Krishnan-Sarin, John H. Krystal, Julia Shi, Brian Pittman, and Stephanie S. O'Malley

...

Secondary analyses found significant inverse effects of naltrexone on drinking in the male drinkers on the basis of FH status. Specifically, after a 100-mg dose of naltrexone, drinking was significantly reduced in male FH+ drinkers but increased in male FH− drinkers. Naltrexone's robust effect in FH+ male drinkers might be related to more complete blockade of opioid receptors (Oswald and Wand 2004). In contrast, although speculative, naltrexone's counter-therapeutic effect in FH− male drinkers could be related to potential FH differences in antagonism of K opioid receptors, an effect that has been shown to increase alcohol drinking (Mitchell *et al*. 2005).



I quickly ran (actually, it was Thanksgiving, so my run was more like a waddle) to my nearest computer and dialed in to PubMed. Had anyone already tested the degree to which naltrexone blockades opioid receptors in alcoholics?

Sure enough, my friend, Else Weerts, had done just that:

Neuropsychopharmacology (2008) 33, 653–665

Differences in δ- and μ-Opioid Receptor Blockade Measured by Positron Emission Tomography in Naltrexone-Treated Recently Abstinent Alcohol-Dependent Subjects

Elise M Weerts*,1, Yu Kyeong Kim2, Gary S Wand1, Robert F Dannals1, Jae Sung Lee2, J James Frost1 and Mary E McCaul

But why hadn't the normally very thorough Elise looked at Naltrexone's blockade of Kappa receptors too?

(Why?)

Afterall, Naltrexone binds to μ, K, and δ opioid receptor subtypes.

Perhaps there was an opportunity here?

...

Naltrexone is a Federal Drug Agency (FDA) approved medication for treatment of alcohol dependence. Two important double-blind placebo-controlled clinical trials (O'Malley et al, 1992; Volpicelli et al, 1992) first demonstrated that, when combined with psychosocial treatment, the nonselective OR antagonist naltrexone reduced craving and the number of alcohol-drinking days in recently abstinent alcoholics. Since then, numerous clinical studies have been conducted. Recent reviews and meta-analyses of these randomized clinical trials indicate that naltrexone is effective in reducing drinking and relapse, however, not all individuals show improvement (Anton and Swift, 2003; Garbutt et al, 1999; Mann, 2004). The optimal dosing regimen, duration of treatment, and identification of individual patient characteristics that predict a successful outcome with naltrexone administration are still under investigation.

Mean [^{11}C]carfentanil BP Images in 21 alcoholics

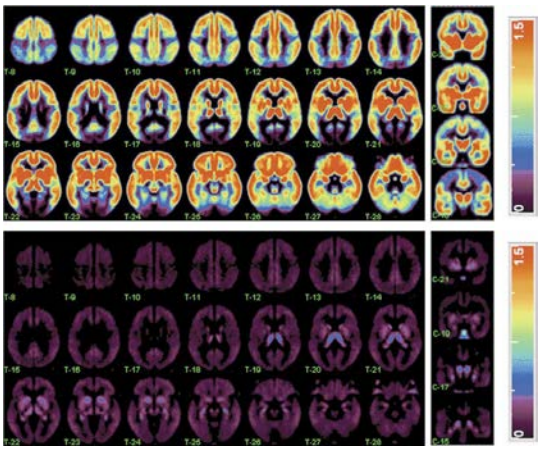


Figure 1 Mean images of the distribution of m-OR in the brain of 21 alcoholics after IV administration of [^{11}C]CAR during scans conducted pre- altrexone treatment (top panel) and during naltrexone treatment (bottom panel). Images shown are color-coded according to the scale shown (0–1.5) so hat highest concentrations of the radiotracer are represented by red and lowest concentrations by black/purple.

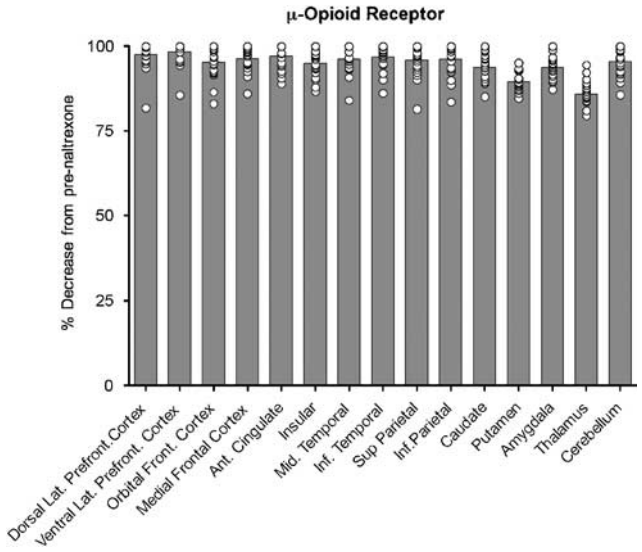


Figure 2 Changes in m-OR BP during treatment with naltrexone. Data are shown as percent decrease from baseline ((Basal-inhibition)/ Basal x 100) across brain regions of interest (ROIs). Bars are group means and data points represent individual subjects.

Why is it unlikely that the degree of blockade of μ by naltrexone is the explanation for naltrexone's efficacy?

Let's think in terms of an NIH grant proposal.
Please keep in mind some key things that NIH grant reviewers are looking for:

Impact on Public Health.
What we need to know is something about mechanism before we can design more effective treatments. Please state how what you propose could impact public health.

Innovation
How can you dig into what Krishnan-Sarin et al. speculated in 2007 (see highlighted text from 2007 paper) while still proposing something novel?

Rationale
Remember, NIH wants proposals that put forth research projects that are based on published findings. **What** about the Weerts paper (2008) suggests that blockade of Mu is not the key to Naltrexone efficacy?

Rigor
NIH does not want unreproducible or irrelevant research. A winning design often combines the identification of an imaging-based biomarker or disease mechanism with further demonstration that the biomarker is directly related to behavior. Ideally, the behavior will be probed using established technique(s)

Assume you do not have any preliminary data that is explicitly of the form that you intend to acquire. That puts you in the realm of an R21.

The R21 budget is limited. $275K in direct costs over 2 years (usually extendable to 3)
- Assume that 40% of direct costs must go to personnel.
- That leaves you with $165K for experiments.
- A PET scan costs $5K
- An MRI scan costs $500
- A subject must be paid $200 to participate in a PET scan
- A subject must be paid $50 to participate in an MR scan

This is admittedly restrictive.
What narrowing of your scope can help fit your project into the budget?
How can you justify your choices?

Now to the assignment(s)

Phase I.

State the specifics of your proposal.

1. What is your AIM(s)?

2. What is your hypothesis?

3. What is the basis for your hypothesis? (Rationale)

4. Design
General Design Considerations.
- What are some of the "don'ts" that we have discussed in class?
- Please take care to avoid them..

Please include a time-line diagram of the experiment(s) you propose.

5. What are the calculated endpoint(s)?

6. What are the second-level analyses needed – if any?

Phase II.

The Chairwoman of your department is an excellent fundraiser and advocate for research. She manages to persuade a forward-thinking philanthropist interested in brain imaging to donate $100 million to the PET center which will be used to subsidize PET scan costs.

If the PET-subsidy fund can be tapped to cut the cost of a PET scan to $1250, how will you expand your proposal? (Additional aims, hypotheses? cohorts?)