Reconsidering the Criterion for Excluding Comorbid Substance Use Disorders from Clinical Trials for the Treatment of Depression

An Analysis of the STAR*D Level One Treatment Outcomes

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INTRODUCTION

Individuals with major depressive disorder (MDD) frequently present with recent or concurrent substance use disorders (SUD, excluding nicotine and caffeine). These comorbid subjects are typically excluded from depression treatment trials, leaving a gap in understanding the treatment outcomes. Clinical trials frequently mandate a lengthy period of remission of SUDs as part of the eligibility criteria. This criterion often leads to more screen failures, which slows enrollment and limits generalizability. Are these criteria based on clear evidence that they serve to enhance the results or safety of a clinical trial? Or, are they based on clinical trial lore or bias?

The prevalence rates of SUD in those with MDD:

- **29% of participants in STAR*D**
- **8.6% to 25% (current SUD) and 30% to 42.8% (lifetime SUD) in MDD treatment-seeking populations**
- **8.5% to 21.4% (current SUD) and 27% to 40% (lifetime SUD) in general population individuals with MDD**

RCTs of pharmacotherapy for MDD with comorbid alcohol dependence:

- **Antidepressants superior to placebo in reducing depression in 6 out of 8**
- **Antidepressants superior to placebo in reducing alcohol use in 3 out of 8**

A meta-analysis of RCTs of antidepressants: Antidepressants exert a modest benefit for patients with MDD and co-occurring SUD

STAR*D METHODS

Adult outpatients with nonpsychotic MDD received treatment with citalopram as first level treatment.

Entry Criteria: ≥14 on 17-item Hamilton Rating Scale for Depression

Exclusion Criteria: SUD in need of immediate detoxification

Psychiatric Diagnostic Screening Questionnaire (PDSQ) = defined comorbid Axis I disorders, including SUD.

Quick Inventory of Depression Scale Self Report (QIDS-SR) = outcome

Clinical Sites: 18 primary care and 23 psychiatric clinics (public & private)

RESULTS

Of 2,876 evaluable STAR*D participants (at least 1 post-baseline visit):

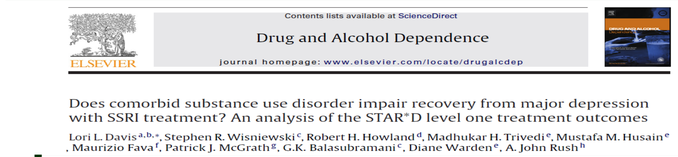
- **29% (n=831) had concurrent SUD**
- **18.9% (n=536) had alcohol use disorder**
- **5.5% (n=155) had drug use disorder**
- **4.9% (n=138) had both alcohol & drug**

Compared to MDD w/o SUD, those SUD+ were more likely to be or have:

- **Male**
- **Younger**
- **Never married**
- **Lower income**
- **Without insurance**
- **Recurrent depression**
- **History of suicide attempts**
- **Positive family history of mood disorder and SUD**
- **Younger age at onset of depression (i.e., an age of onset ≤18 years)**
- **Higher number of Axis I comorbidities (especially anxiety disorders)**

These differences were strongest in the group that endorsed both alcohol and drug use disorder compared to the MDD w/o SUD group.

RESULTS



Does comorbid substance use disorder impair recovery from major depression with SSRI treatment? An analysis of the STAR*D level one treatment outcomes

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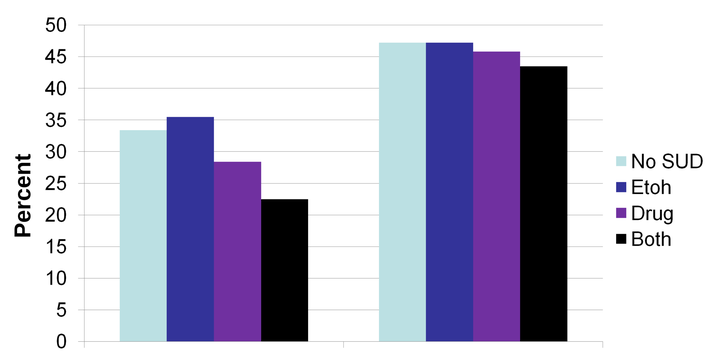
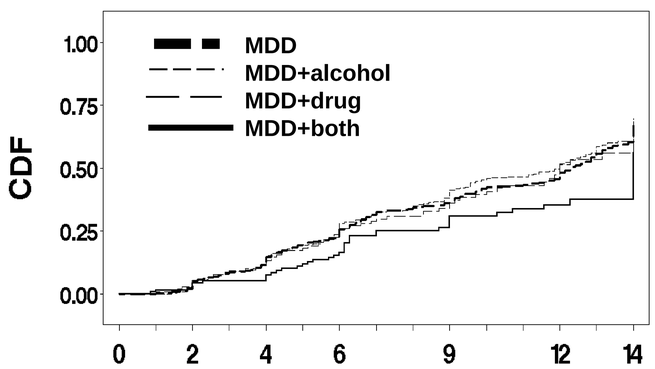
Rates of Response and Remission



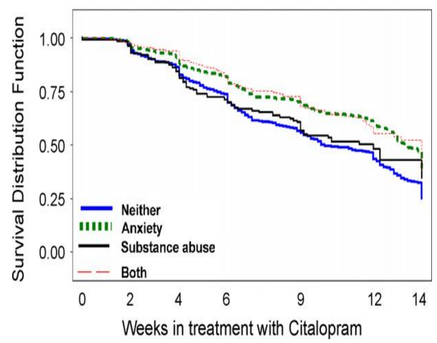
33.4% MDD without SUD remitted
35.5% MDD with alcohol use remitted
28.4% MDD with drug use remitted
22.5% MDD with both alcohol and drug remitted
(p= 0.02; *MDD with both were 42% less likely to remit)*
47% achieved response
No differences b/w groups in rate of or time to response.

Time to Remission Longer if Both Drug and Alcohol



SAE and AE: No differences between groups in medication intolerance, frequency, intensity or burden of side effects. Proportion of any SAE was similar between groups; however, SUD+ were significantly more likely to have psychiatric SAE (3.3% vs. 1.5%) and MH hospitalization (2.8% vs. 1.2%). The number of deaths was very low (n=3); however, all deaths occurred in the SUD+ group (2 alcohol-only MDD & 1 drug-only MDD; (deaths due to cancer, fall-induced subdural hematoma, and homicide).

ADDITIONAL STAR*D FINDINGS



	REMIT (%)	RESPOND (%)
MDD	40	52
MDD & Anxiety	28	43
MDD & SUD	33	45
MDD & Anx+ SUD	25	43

Time to Remission significantly longer in group of MDD & anxiety disorder and group of MDD& anxiety disorder+SUD compared to MDD group and MDD+SUD.

Rate of response and remission significantly less for MDD&Anx+SUD and MDD&Anx group compared to MDD group and MDD+SUD groups.

Howland R. et al. Drug and Alcohol Dependence 2009.

Overall in STAR*D, 26% of enrolled participants exited early for non-medical reasons. Attriters were more likely to be younger, less educated, in their first MDD episode, African American, Hispanic, publically insured, and having a greater number of Axis I comorbidities (especially 3 or more). Less attrition was associated with more years since the onset of first MDE. (*Warden D. et al. 2009.) However, in our study, the MDD and MDD+SUD groups did not differ in dose or length of treatment with citalopram.*

In STAR*D ancillary study, rates of response (46%) and remission (32%) in subjects with MDD and alcohol use disorder did not significantly differ from those without (response 47%, remission 34%). (*McGrath P. et al submitted).*

CONCLUSIONS

Despite baseline clinical and demographic differences, a concurrent drug or alcohol use disorder does not necessary impact the response to antidepressant treatment in clinical trials. However, the increased burden of having both an alcohol and drug use disorder or having a concurrent anxiety disorder and SUD may have impact on response and remission. Conceptualizing inclusion criteria that allow entrance of some, but not all, subjects with SUD into depression treatment trials is possible with these data.

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