Helpful or Harmful?
The use of SSRIs in Alcohol Use Disorder

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Learning Objectives
1. Discuss the occurrence and implications of comorbid psychiatric illness and substance use disorders
2. Understand the potential role of serotonin in alcohol use disorder
3. Evaluate the literature for the use of selective serotonin reuptake inhibitors (SSRIs) in alcohol dependence subtypes
4. Formulate evidence-based conclusions regarding the use of SSRIs in alcohol dependence subtypes
Dual Diagnosis

I. Definitions\(^1\)\(^2\)\(^3\)
   a. Dual Diagnosis
      i. Mental illness with comorbid substance use disorder (SUD)
      ii. Primary depression: depression preceded SUD or persisted during abstinence
      iii. Secondary depression: substance induced depression
   b. Major Depressive Disorder (See Appendix A)
      i. Persistent feeling of sadness and/or loss of interest or pleasure for at least 2 week period
   c. Problem Drinker
      i. Men: > 7 drinks per week or > 3 drinks per occasion
      ii. Women: > 14 drinks per week or > 4 drinks per occasion
   d. Alcohol Use Disorder (See Appendix A)
      i. A problematic pattern of alcohol use leading to clinically significant impairment or distress

II. Epidemiology of Dual Diagnosis\(^4\)\(^5\)
   a. In 2011, 18.9 million adults in the United States had SUD, and 41.4 million adults had mental illness
      i. Of those, 6.8 million adults experienced both SUD and mental illness
   b. Male > Female
   c. Severely mentally ill patients followed for one year had higher rates of readmission if dually diagnosed
   d. Drug and alcohol use in mentally ill patients is a strong predictor of homelessness

   Figure 1: Past Year SUD and Mental Illness among Adults Aged 18 or Older: 2011\(^4\)


III. Consequences of Dual Diagnosis\(^6\)
   a. Poor medication compliance
   b. Physical comorbidities
   c. Poor health and/or self-care
   d. Increased risk of suicide or risky behavior
   e. Possible incarceration

IV. Etiologic Theories of Depression and Alcohol Use Disorder\(^5\)\(^6\)
   a. Depression with comorbid alcohol use
      i. Depression may elevate the risk to develop a secondary alcohol use disorder
      ii. Driven to self-medicate with alcohol
   b. Alcohol use with comorbid depression
      i. Alcohol intoxication and continuous alcohol use may prevent remission of depression
      ii. Biopsychosocial consequences of alcohol use disorder may provoke secondary depression
   c. Genetic vulnerability
V. Treatment of Depression and Alcohol Use Disorder
   a. Pharmacologic
      i. Antidepressant plus either naltrexone, disulfiram, or acamprosate
   b. Non-pharmacologic
      i. Self-help groups
      ii. Supportive therapy
      iii. Cognitive Behavioral Therapies (CBT)
      iv. Psychodynamic therapies

VI. Current and Historic Treatment of Dual Diagnosis

Historically
- Separate, uncoordinated treatment of mental illness and SUD
- High readmission rates

Currently
- Integrated treatment for dual diagnosis
- Increased retention and decreased hospitalization

Mid-1980’s
- Dual Diagnosis
- Substance use is more than a manifestation of mental illness

Effects of SSRIs in Alcohol Use Disorders

I. Serotonin’s Functions in the Brain
   a. Serotonin – regulates mood, arousal, cognition, aggression, and impulsivity
   b. Raphe nucleus – project neurons to many brain regions, including the amygdala and nucleus accumbens
   c. Amygdala – important role in the control of emotions
   d. Nucleus accumbens – involved in controlling motivation to perform certain behaviors, including abuse of alcohol and other drugs

Figure 2: Functions of Serotonin in the Brain

- The axon endings of the serotonergic neurons secrete serotonin when activated in these brain regions
II. **Serotonergic Pathways in Alcohol Use**\(^{10,11}\)
   a. **Acute alcohol exposure** → increased serotonin (5HT) in synapse
   b. **Chronic alcohol exposure** → decreased 5HT release and activity at 5HT receptors → up-regulation of 5HT receptors to compensate for continuous inhibition and re-establish homeostasis

<table>
<thead>
<tr>
<th>Alcohol Use</th>
<th>Alcohol Quantity</th>
<th>Serotonergic Effects</th>
<th>Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve/Sober</td>
<td>No Alcohol</td>
<td>![down]</td>
<td>Baseline</td>
</tr>
<tr>
<td>Acute</td>
<td>![40mg/day]</td>
<td>![down] ![up]</td>
<td>Intoxication/Sedation</td>
</tr>
<tr>
<td>Chronic/</td>
<td>![40mg/day] ![60mg/day]</td>
<td>![down] ![up] ![up]</td>
<td>Up-regulation/New baseline</td>
</tr>
<tr>
<td>Tolerance</td>
<td>![40mg/day] ![60mg/day]</td>
<td>![down] ![up] ![up]</td>
<td>Withdrawal/Cravings</td>
</tr>
<tr>
<td>Abstinent</td>
<td>![40mg/day] ![60mg/day]</td>
<td>![down] ![up] ![up]</td>
<td></td>
</tr>
</tbody>
</table>

= alcohol;  = no alcohol;  = serotonin;  = serotonin receptor

III. **Studies Evaluating the Use of SSRIs for Alcohol Use Disorder**
   a. **Problem drinkers without comorbid depression**\(^{12,13}\)
      i. 12-week randomized-controlled trial (RCT) comparing citalopram 20 or 40 mg/day to placebo
         1. Statistically significant decrease in the number of drinks consumed and increase in number of days abstinent with citalopram 40 mg/day
      ii. 6-week RCT comparing 40 or 60 mg/day of fluoxetine to placebo
         1. Fluoxetine 60 mg/day significantly decreased total number of drinks consumed, but no significant effect on total number of days abstinent
   b. **Alcohol dependence without comorbid depression**\(^{14}\)
      i. 12-week RCT comparing fluoxetine (up to 60 mg/day) to placebo plus weekly psychotherapy
         1. No statistical significance between fluoxetine and placebo in reducing alcohol consumption
   a. **Meta-analyses with comorbid depression and alcohol use disorder**
      i. Systemic review \(^{15}\) of RCTs from 1966 to 2004 on the efficacy of antidepressant drugs in subjects with SUDs (alcohol, cocaine, nicotine and opioid, with and without comorbid depression)
         1. Alcohol use disorder without depression
            a. Antidepressants are not justified in alcohol use disorder without depression
            b. Seven RCTs included, reduction of alcohol use was not significant for SSRIs (OR = 1.83; 95% CI 0.75-4.46), or other antidepressants (OR = 1.85; 95% CI 0.26-13.19)
         2. Alcohol use disorder with depression
            a. No significant advantage for the use of SSRIs, but a significant effect with other antidepressants
            b. Four RCTs showed no significant reduction in depression with SSRIs (OR = 1.85; 95% CI 0.73-4.68), however, three RCTs with other antidepressants showed a significant difference in depressive symptoms (OR = 4.15; 95% CI 1.35-12.75)
            c. No significant difference in alcohol use with SSRIs (OR 0.93; 95% CI 0.45-1.91) or other antidepressants (OR 1.99; 95% CI 0.78-5.08)
      ii. Meta-analysis\(^{16}\) of 11 RCTs from 1980 to 2009 reviewed depression/dysthymic disorder with comorbid alcohol use disorder
         1. No significant difference in relative efficacy of SSRIs versus placebo (p=0.973)
         2. Tricyclic antidepressants and nefazodone were more effective than placebo (RR of response = 1.336; p=0.021)
IV. Subgroup Effects

a. Primary goal of typology\textsuperscript{17, 18}
   i. Match patient subtype with the most effective and targeted treatment strategy

b. Cloninger’s Typology I and II\textsuperscript{19, 20}
   i. Personality theory
      1. Based on the personality of the alcohol dependent patient
      2. Exclusively male patients

c. Babor’s Typology A and B\textsuperscript{21, 22}
   i. Cluster analysis
      1. Based on 321 alcohol dependent patients at US treatment facilities
      2. Statistical analysis produced 17 domains
         a. Personality traits, co-morbid psychiatric disorders, severity of consumption of alcohol and other substances, family history of alcoholism, and consequences of alcohol consumption
      3. Consisted of both male and female patients
   ii. Schuckit et al.\textsuperscript{23} simplified the classification scheme to include 5 of the 17 domains as an abbreviated approach to a clinical setting
      1. Ounces of alcohol consumed per day, drinking to relieve negative affect, medical conditions, physical and social consequences

Table 2: Distinguishing Characteristics of Cloninger’s Typology I and II\textsuperscript{19, 20}

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-onset (&gt; 25 years)</td>
<td>Early-onset (≤ 25 years)</td>
</tr>
<tr>
<td>Men = Women</td>
<td>Men &gt; Women</td>
</tr>
<tr>
<td>Strong influence of social environment factors</td>
<td>Strong genetic influence</td>
</tr>
<tr>
<td>Influenced by childhood family environment</td>
<td>Uninfluenced by childhood family environment</td>
</tr>
<tr>
<td>Ability to abstain from drinking</td>
<td>Inability to abstain from drinking</td>
</tr>
<tr>
<td>Desire to avoid harm</td>
<td>No desire to avoid harm</td>
</tr>
<tr>
<td>Avoids heavy drinking</td>
<td>Often drinks heavily</td>
</tr>
<tr>
<td>Self-medicate with alcohol</td>
<td>Drink for pleasure</td>
</tr>
<tr>
<td>Respond better to treatment</td>
<td>Poor response to treatment</td>
</tr>
</tbody>
</table>

c. Early-onset alcoholism (EOA) vs. late-onset alcoholism (LOA)\textsuperscript{17}
   i. Contrast between early (Type II/Type B) and late (Type I/Type A)
      1. Simpler classification of two typology classifications
         a. Age of onset (≤ 25 years vs. > 25 years)
         b. Careful history of self-reported problems related to drinking
      2. Effective predictor of response to treatment with serotonergic medications

Table 3: Distinguishing Characteristics of Babor’s Typology A and B\textsuperscript{21, 22}

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-onset (&gt; 30 years)</td>
<td>Early-onset (≤ 21 years)</td>
</tr>
<tr>
<td>Fewer childhood risk factors</td>
<td>More childhood risk factors</td>
</tr>
<tr>
<td>Less severe symptoms</td>
<td>Familial alcoholism</td>
</tr>
<tr>
<td>Less psychopathology</td>
<td>More psychopathology</td>
</tr>
<tr>
<td>Less stress</td>
<td>More life stress</td>
</tr>
<tr>
<td>Less chance of prior treatment</td>
<td>Chronic treatment history</td>
</tr>
<tr>
<td>Fewer alcohol-related social &amp; physical consequences</td>
<td></td>
</tr>
</tbody>
</table>
V. Functional Polymorphisms
   a. Serotonin transporter gene (SLC6A4 or SERT or 5-HTT)
      i. Codes for the serotonin reuptake protein and removes serotonin from the synapse
      ii. Principle site of action for SSRIs
      iii. Genetic mutations of the 5-HTT linked promoter region (5-HTTLPR) are associated with response to antidepressants
         1. Short allele (SS)
            a. Produce less mRNA and have less serotonin transporter expression
         2. Long allele (L)
            a. L6 or LL homozygous
               i. Produce more mRNA and have more serotonin transporter expression
            b. L4 or LS heterozygous
               i. Reduced mRNA expression equivalent to that of the SS allele

Figure 3: SLC6A4 location and allelic variation of serotonin transporter polymorphisms

Adapted from Canli and Lesch, with permission from the Nature Publishing Group

VI. Studies Evaluating Functional Polymorphisms in Alcohol Use Disorder
   a. 5-HTTLPR polymorphisms on alcohol cravings
      i. Higher compulsive cravings seen in LL-carriers of the 5-HTTLPR polymorphism
   b. EOAs vs. LOAs and 5-HTTLPR polymorphisms on drinking behavior
      i. A study by Kranzler et al. in 2011 found no effects among SS-carriers; however, in LL-carriers, the effects varied by age of onset (p=0.002)
         1. LOAs reported fewer drinking and heavy drinking days with sertraline (p=0.011)
         2. EOAs had fewer drinking and heavy drinking days with placebo (p<0.001)
      ii. EOA LL-carriers appear to have higher alcohol cravings than SS-carriers; however, the opposite is true with LOA LL-carriers, who have less alcohol cravings
Clinical Trials

Fluoxetine treatment seems to reduce the beneficial effects cognitive-behavioral therapy in type B alcoholics\(^{14, 28}\)


<table>
<thead>
<tr>
<th>Design</th>
<th>12 week, double-blind, placebo-controlled clinical trial; re-analysis</th>
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</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Fluoxetine treatment would differentially reduce drinking among type B subjects</td>
</tr>
</tbody>
</table>
| Patient Population | • Met DSM-III-R criteria for alcohol dependence  
                      • Had no substantial physical or laboratory abnormalities |
| Intervention    | • Patients were randomized to two treatment groups: fluoxetine up to 60 mg/day or placebo; each of which contained 25 mg of riboflavin to facilitate compliance monitoring  
                      • Dose selection: As tolerated, the dose of fluoxetine was increased every 3-4 days by one additional 20 mg capsule to a maximum of 60 mg/day  
                      • Assessment: Patients were assessed at the time of study enrollment, at the end of the 12 week treatment phase, and at 6 months after the end of treatment |
| Endpoints       | Primary endpoints:  
                      • Number of drinking days  
                      • Average number of drinks per day |
| Statistical Analysis | • Analysis of variance (ANOVA)  
                      • Multivariate analysis of covariance (MANCOVA)  
                      • Last observation carried forward (LOCF) used to analyze drinking data for subjects who did not complete the 12-week study |
| Results         | Pretreatment to Treatment Endpoint Comparisons: |

<table>
<thead>
<tr>
<th>Table 7: Drinking Measures During Pretreatment and Treatment Endpoints by Alcoholic Subtype and Medication Group, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type A</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>Drinking days</td>
</tr>
<tr>
<td>Drinks per day</td>
</tr>
<tr>
<td>GGTP*</td>
</tr>
</tbody>
</table>

PreTx = Pretreatment; EndPt = Treatment Endpoint; *GGTP = γ-glutamyltranspeptidase

- No effect of alcoholic subtype or medication group on drinking-related outcomes
- There was a significant effect of treatment completion on these measures (\(p < 0.001\)); treatment completers reported a greater decrease from pretreatment levels, compared with non-completers, in drinking days (\(\Delta = -41.6\) vs. -28.6; \(p < 0.001\)), drinks per day (\(\Delta = -6.7\) vs. -4.7; \(p < 0.00\)), and GGTP levels (\(\Delta = -18.6\) units vs. -7.4 units; \(p = 0.005\))
- There was also a significant interaction of alcoholic subtype and medication group (\(p=0.031\)); effect was consistent across all three drinking measures, however, was only significant for GGTP level (\(p=0.022\))
  - Among type B subjects, the decrease in GGTP level from baseline to treatment endpoint was greater (\(p=0.065\)) for those receiving placebo (\(\Delta = -28.1\) units) than for those receiving fluoxetine (\(\Delta = -13.9\))
  - Effect of medication group was not significant among type A alcoholics (\(p=0.11\))
- None of the other interactions had significant effects on the outcomes
### Results, continued

Six-Month Post-treatment Follow-up Comparisons:
- There was no effect of alcoholic subtype or medication group on drinking-related outcomes during the follow-up period; there was a non-significant trend for an effect of treatment completion (p=0.081), with drinking-related outcomes favoring those subjects who completed the treatment phase of the study.
- There were no significant effects of any interactions on these measures at follow-up.
- Of the 95 patients who were included in the subtyping analysis, 93 (98%) were interviewed at the end of treatment.
- A total of 85 patients (89%) were interviewed at 6-month post-treatment follow-up visit.

### Authors

**Conclusions**

In the absence of a comorbid mood or anxiety disorder, fluoxetine should not be used to maintain abstinence or reduce drinking in high-risk/severity alcoholics. A multivariate approach to treatment matching may be feasible in the context of routine clinical care.

### Comments and Conclusions

**Strengths:**
- Study design – 12 week, double-blind, placebo-controlled clinical trial; re-analysis

**Limitations:**
- Re-analysis
- Use of a 60-day timeframe for the self-reported drinking measures may have reduced the validity of these measures

**Conclusions:**
- Alcoholic subtypes identified by cluster analysis seem to be differentially responsive to the effects of fluoxetine treatment on drinking-related outcomes.
- Serotonergic abnormalities among a subgroup of alcoholics who are also characterized by impulsivity and severity of alcohol dependence may help explain the differential medication effect.

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### Sertraline treatment for alcohol dependence. Interactive effects of medication and alcoholic subtype


**Design**

14 week, prospective, double-blind, placebo-controlled clinical trial

**Objective**

Evaluate the efficacy of sertraline in the treatment of patients with alcohol dependence, subgrouped on the basis of presumed 5-HT dysfunction or absence thereof

**Patient population**

- 18 years of age or older
- Met DSM-III-R criteria for alcohol dependence
- With or without a lifetime DSM-III-R diagnosis of major depression
- Actively drinking in the preceding 30 days
- Seeking treatment

**Intervention**

- Patients were randomized to two treatment groups: sertraline titrated up to 200 mg/day as tolerated or placebo; riboflavin 100 mg was included in daily dose to facilitate compliance monitoring
- Assessment: All patients received weekly sessions of therapy for 14 weeks

**Endpoints**

**Primary endpoint:**
- The number of weeks to relapse (5 or more drinks in one day)
- The percent days drinking during treatment
- The proportion of subjects who maintained continuous abstinence over the 14 weeks of treatment

**Statistical Analysis**

- Cox regression survival analysis
- Median rank test
- ANCOVA in post-hoc subgroup comparisons
Primary endpoints:

Number of weeks to relapse:
- The number of weeks to relapse for Type A sertraline versus placebo was 5 versus 4 weeks, respectively; for Type B, sertraline versus placebo was 3.7 versus 3.8 weeks
- No medication effect (p=0.86), but there was a significant difference in the time to relapse between alcoholic subtypes, such that Type A patients took longer to relapse than Type B patients (p=0.013)
- The interaction between medication and alcoholic subtype was not significant (p=0.11)

Percent days drinking during treatment:
- No significant difference in percent days drinking during treatment was found by alcohol subtype (p=0.81) or medication group (p=0.23), but there was a significant interaction between medication condition and alcoholic subtype (p=0.05)
- Type A patients on sertraline was associated with fewer days drinking compared to placebo: the median percent days drinking in-trial for Type A sertraline versus placebo was 0% versus 22.4% days, respectively (p=0.01)
- There was no statistical difference in the contrast between sertraline and placebo-treated patients in the higher risk/severity (Type B) patients in this sample: Type B sertraline versus placebo was 8.2% versus 4.1% days, respectively (p=0.46)

Proportion of subjects who maintained continuous abstinence over 14 weeks of treatment:
- There were more lower risk/severity (Type A) patients with continuous abstinence during treatment than higher risk/severity (Type B) patients
- Type A sertraline versus placebo patients were significantly more likely to maintain continuous abstinence for the 14 weeks of treatment compared to those taking placebo: 53.3% versus 16%, respectively (p=0.004)
- There was no statistical difference in the contrast between sertraline and placebo-treated patients in the Type B patients; results for Type B, sertraline versus placebo, were 10% versus 24%, respectively (p=0.22)
SSRIs could be considered a potentially viable strategy for reducing alcohol consumption, but that they should be used judiciously and the patient’s progress should be closely monitored, particularly among patients with multiple features typical of Type B (higher risk/severity) alcohol dependence.

**Authors Conclusions**

**Comments and Conclusions**

- **Strengths:**
  - Study design - 14 week, prospective, double-blind, placebo-controlled clinical trial

- **Limitations:**
  - Limited generalizability due to self-reporting and clinical trial treatment setting
  - Limited identification or classification of subjects with potential 5-HT abnormalities

- **Conclusions:**
  - Finding suggest that a multivariate approach to subtyping (Type A and B), may be important for evaluating the effects of sertraline in the treatment of alcohol dependence

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**Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology**


**Design**

- 52 week, prospective, randomized, placebo-controlled, multicenter study in parallel groups

**Objective**

- **Primary aims:** (1) to test fluvoxamine’s efficacy in reducing relapse in newly detoxified alcohol dependent patients; (2) to examine fluvoxamine’s efficacy, relative to placebo, in alleviating symptoms of depression and anxiety associated with abstinence in alcohol dependence; and (3) to investigate fluvoxamine’s safety in the long-term treatment of alcohol dependence

- **A priori secondary aim:** examine the interaction between pharmacotherapy, outcome, and type of patient defined either according to age of onset regular drinking or of problem drinking, or to the typology

**Patient Population**

- Age 21 years of age and older
- Diagnosis of alcohol dependence (using DSM-III-R diagnostic criteria)
- Detoxified and abstinent for 10-30 days

**Intervention**

- Randomization within centers occurred, in blocks of eight, four patients per block to each treatment
- **Dose selection:** A fluvoxamine dose of 100-300 mg per day, with the intention to give doses at the higher end of this range if well tolerated plus psychotherapy
- **Assessment:** Patients were assessed after detoxification on the day of randomization, and after 2, 4, 6, 8, 12, 16, 24, 32, 40 and 52 weeks of treatment

**Endpoints**

- **Primary endpoints:**
  - The proportion of patients abstinent since the last assessment
  - The proportion of patients not relapsing to uncontrolled drinking since baseline (defined as 5 or more units on an occasion and 4 or more such occasions in a week, or 12 or more units on an occasion (Unit = 9 g ethanol))
  - Alcohol dependence severity index (based on the sum of the symptoms listed in DSM-III-R criteria)
  - The proportion of days not drinking since last assessment

**Statistical Analysis**

- **Primary endpoints:**
  - ANCOVA
  - Ordinal data: Logistic regression

- **Continuous data:**
  - $t$-test
  - Parametric analysis of variance

- **Binary data:**
  - Chi-square test
  - Logistic regression
Chick, et al. 2004 continued

Results

<table>
<thead>
<tr>
<th>Primary endpoints:</th>
<th>Completely abstinent since last assessment</th>
<th>Not relapsed since baseline</th>
<th>Mean dependence severity (1-6)</th>
<th>Days not drinking since last assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 4: Primary efficacy variables</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LOCF*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>Fluvoxamine (n=243)</td>
<td>42%</td>
<td>54%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Placebo (n=249)</td>
<td>46%</td>
<td>60%</td>
<td>2.5%</td>
<td>77%</td>
</tr>
<tr>
<td>(p)-value</td>
<td>0.4</td>
<td>0.18</td>
<td><strong>0.029</strong></td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Week 52</td>
<td>Fluvoxamine (n=243)</td>
<td>29%</td>
<td>36%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Placebo (n=249)</td>
<td>29%</td>
<td>36%</td>
<td>3.5%</td>
<td>62%</td>
</tr>
<tr>
<td>(p)-value</td>
<td>0.94</td>
<td>0.47</td>
<td>0.42</td>
<td>0.13</td>
</tr>
<tr>
<td>Observed cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>Fluvoxamine (n=151)</td>
<td>50%</td>
<td>64%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Placebo (n=192)</td>
<td>54%</td>
<td>69%</td>
<td>2%</td>
<td>87%</td>
</tr>
<tr>
<td>(p)-value</td>
<td>0.46</td>
<td>0.38</td>
<td>0.087</td>
<td>0.081</td>
</tr>
<tr>
<td>Week 52</td>
<td>Fluvoxamine (n=75)</td>
<td>55%</td>
<td>55%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Placebo (n=117)</td>
<td>63%</td>
<td>63%</td>
<td>2.3%</td>
<td>88%</td>
</tr>
<tr>
<td>(p)-value</td>
<td>0.24</td>
<td>0.24</td>
<td>0.75</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*LOCF = last observation carried forward
- In the LOCF analysis, at Week 12 the percentage of days not drinking since last assessment and mean dependence severity were significantly more favorable for the placebo group
- In the observed cases analysis, there were statistically non-significant trends (\(p < 0.1\)) at Week 12 for these two measures in favor of placebo
- No statistically significant differences between the two treatment groups at Week 52 endpoint for any of the four primary efficacy variables

**Typology by Tridimensional Personality Questionnaire (TPQ) score:**

<table>
<thead>
<tr>
<th></th>
<th>Fluvoxamine (n=260)</th>
<th>Placebo (n=260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Type II</td>
<td>Type I</td>
</tr>
<tr>
<td>n=131</td>
<td>n=114</td>
<td>n=135</td>
</tr>
<tr>
<td>13.7%</td>
<td><strong>6.14%</strong></td>
<td>19.3%</td>
</tr>
</tbody>
</table>

*Chi-square test: \(p=0.0172\); Log rank test: \(p=0.000602\)
### Chick, et al. 2004 continued

<table>
<thead>
<tr>
<th>Results, continued</th>
<th>Multiple logistic regression:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 243 patients who reported starting regular drinking below age 25, of those 130 had their first problems before that age, concordance between these parameters being low</td>
</tr>
<tr>
<td></td>
<td>• There was little concordance between TPQ score (high/low) and start of regular drinking (below/at or after 25 years) and age of onset of problems (below/at or after 25 years)</td>
</tr>
<tr>
<td></td>
<td>• Age of start of regular drinking was slightly stronger predictor of relapse at 52 weeks (p=0.0224) than age of onset of problems (p=0.0537)</td>
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<tr>
<td></td>
<td>• Males tended more often than females to report an onset of regular drinking and of problems before age 25</td>
</tr>
<tr>
<td></td>
<td>• Gender affected patients’ response to treatment, males responding better to placebo than fluvoxamine which was an interaction that was not seen for females (p=0.0052; Week 52 data)</td>
</tr>
<tr>
<td></td>
<td>• For age of start of regular drinking, adjusting for gender does not significantly reduce the interaction; fluvoxamine patients are still more likely to have relapsed at 52 weeks than placebo patients (p=0.0117)</td>
</tr>
</tbody>
</table>

| Authors Conclusions | Unless there is an over-riding clinical reason such as specific psychiatric co-morbidity, caution should be exercised in the use of SSRIs in patients whose regular drinking commenced before age 25 or who report problems from their drinking before age 25. |

<table>
<thead>
<tr>
<th>Comments and Conclusions</th>
<th>Strengths:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Study design - 52 week, prospective, randomized, placebo-controlled, multicenter study in parallel groups</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comments and Conclusions</th>
<th>Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• There was variation between sites in the study in the psychosocial intervention received by the patients, which could have been a confounder</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comments and Conclusions</th>
<th>Conclusions:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• No evidence that fluvoxamine helps prevent relapse in detoxified, abstinent, alcoholics</td>
</tr>
<tr>
<td></td>
<td>• Fluvoxamine was associated with worse outcomes than placebo for early-onset drinkers, or Type II based on TPQ scores</td>
</tr>
</tbody>
</table>

---

**Serotonin transporter polymorphism as a predictor for escitalopram treatment of major depressive disorder comorbid with alcohol dependence**


<table>
<thead>
<tr>
<th>Design</th>
<th>26 week, randomized, double-blind clinical trial; re-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>To examine associations between 5-HTTLPR and Montgomery-Asberg Depression Rating Scale (MADRS)/Alcohol Use Disorders Identification Test (AUDIT) over the whole treatment period and secondarily during the specific periods of treatment</td>
</tr>
<tr>
<td>Patient Population</td>
<td>• Men and women aged 26 to 65 years old</td>
</tr>
<tr>
<td></td>
<td>• History of heavy drinking (5 or more daily drinks for men and 4 or more daily drinks for women) for at least 10 years</td>
</tr>
<tr>
<td></td>
<td>• Significant depression (defined by Beck Depression Inventory-II score &gt; 17)</td>
</tr>
<tr>
<td></td>
<td>• Interested in voluntarily taking part in the study</td>
</tr>
<tr>
<td>Intervention</td>
<td>• Patients were randomized in two groups: escitalopram 20 mg daily and memantine 20 mg daily</td>
</tr>
<tr>
<td></td>
<td>• Titration: Both groups were started at 5 mg/day, increasing dose weekly to 20 mg daily</td>
</tr>
<tr>
<td></td>
<td>• Side effect management: After four weeks, the study physician was allowed to decrease the dose in the case of adverse events</td>
</tr>
<tr>
<td></td>
<td>• Compliance: Study medication was ensured with pill count from returned empty blister-packs</td>
</tr>
</tbody>
</table>
Endpoints

Primary endpoint:
- Changes in MADRS scores at months 0, 1, 3, and 6
- Changes in AUDIT scores at months 0, 3, and 6
- Interactions between treatment and genotype

Secondary endpoint:
- Whether 5-HTTLPR genotype predicted change in MADRS and AUDIT scores at certain treatment periods

Statistical Analysis
- Mixed linear model analysis
- Multiple linear regression analysis

Results

Genotype Results:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Escitalopram</th>
<th>Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td>LL allele</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>SL/SS allele</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>SL allele</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>SS allele</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Primary endpoints:

MADRS Scores:
- No associations between 5-HTTLPR genotype and global change in the MADRS scores over the four measurements after adjusting for the medication
- No statistical difference was found in associations of 5-HTTLPR genotype and MADRS scores between escitalopram and memantine groups
- No associations existed between 5-HTTLPR genotype and MADRS scores over the four measurements in either medication group

AUDIT Scores:
- No associations existed between 5-HTTLPR genotype and global change in the AUDIT scores over the four measurements after adjusting for the medication group
- There were no statistical differences in associations of 5-HTTLPR genotype and AUDIT scores between escitalopram and memantine groups
- No associations existed between 5-HTTLPR genotype and AUDIT scores over the three measurements in either medication group

Secondary endpoints:

Figure 6: Change is MADRS scores during the 26 week treatment according to 5-HTTLPR genotypes
Muhonen, et al. 2011 continued

Results, continued

- The LL genotype was associated with greater decrease in MADRS scores between 3 and 6 months in the escitalopram group (p=0.03)
- The LL genotype was associated with lower MADRS scores at 6 months after adjusting for the baseline MADRS score in the escitalopram group (p=0.04); the decrease being on average 20% greater in the LL group than in the other genotypes combined
- In the memantine group, no associations between LL genotype and MADRS decrease between any two measurements were detected
- In analyses of time-specific changes between two consecutive measurements, no associations between AUDIT and genotype in either medication groups were detected

Authors

Conclusions

The L allele of the 5-HTTLPR polymorphism is associated with the responsiveness to escitalopram treatment among patients with major depression comorbid with alcohol dependence, especially after a 3 month treatment period. Larger prospective studies lasting at least 6 months are warranted to confirm these preliminary results.

Comments & Conclusions

Strengths:
- Study population represents treatment-seeking alcohol-dependent patients comorbid with major depression in three municipal care units without any patient selection
- Conducted by one psychiatrist researcher in a double-blind setting eliminating the differences in estimations between researchers

Limitations:
- Re-analysis
- Total number of patients in the study is relatively low
- Small amount of SS genotypes in the study sample
- Small amount of LL genotypes in the memantine group
- No typology completed

Conclusions:
- Treatment response may vary according to the 5-HTTLPR genotype in patients with major depressive disorder comorbid with alcohol dependence
- The LL allele of the 5-HTTLPR polymorphism appears to have an increased responsiveness to escitalopram treatment compared to the SS and SL alleles combined
- The 5-HTTLPR polymorphism did not affect the response to memantine

Conclusions

- Type II, Type B, SS/SL allele polymorphisms all appear to have a negative response to SSRIs
- Type I, Type A, LL allele polymorphisms all appear to respond favorably to treatment with SSRIs
- EOA vs. LOA typology is a quick way to assess for potential efficacy of SSRIs
- Given the common diagnosis of comorbid depression and alcohol use disorder, typology should be assessed in every patient prior to starting treatment with SSRI antidepressants
- Larger prospective RCTs lasting at least 6 months are needed
Appendix A: Diagnostic and Statistical Manual (DSM) Diagnostic Criteria\textsuperscript{1,32,33}

<table>
<thead>
<tr>
<th>DSM-III-R</th>
<th>DSM-IV-TR</th>
<th>DSM 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychoactive Substance Abuse</strong></td>
<td><strong>Substance Abuse</strong></td>
<td><strong>Alcohol Use Disorder</strong></td>
</tr>
<tr>
<td>A. A maladaptive pattern of substance use leading to at least one of the following:</td>
<td>A. Maladaptive pattern of substance use leading to clinically significant impairment or distress</td>
<td>A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:</td>
</tr>
<tr>
<td>1. continued use despite knowledge of having a persistent or recurrent social, occupational, psychological, or physical problem that is caused or exacerbated by use of the psychoactive substance</td>
<td>1. Recurrent failure to fulfill major role obligations (e.g., work, school, home)</td>
<td>1. Alcohol is often taken in larger amounts or over a longer period than was intended</td>
</tr>
<tr>
<td>2. Recurrent use in situations in which use is physically hazardous (e.g., driving while intoxicated)</td>
<td>2. Recurrent use in physically hazardous situations (e.g., driving)</td>
<td>2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use</td>
</tr>
<tr>
<td>B. Some symptoms of the disturbance have persisted for at least one month, or have occurred repeatedly over a longer period of time</td>
<td>3. Recurrent substance-related legal problems</td>
<td>3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects</td>
</tr>
<tr>
<td>C. Never met the criteria for Psychoactive Substance Dependence for this substance</td>
<td>4. Continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance</td>
<td>4. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home</td>
</tr>
<tr>
<td><strong>Psychoactive Substance Dependence</strong></td>
<td></td>
<td>5. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol</td>
</tr>
<tr>
<td>A. At least three of the following:</td>
<td></td>
<td>6. Craving, or a strong desire/urge to use alcohol</td>
</tr>
<tr>
<td>1. Substance often taken in larger amounts or over a longer period than the person intended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Persistent desire or one or more unsuccessful efforts to cut down or control substance use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. A great deal of time spent in activities necessary to get the substance, taking the substance, or recovering from its effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Frequent intoxication or withdrawal symptoms when expected to fulfill major role obligations at work, school, or home, or when substance use is physically hazardous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Important social, occupational, or recreational activities given up or reduced because of substance use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Continued substance use despite knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by the use of the substance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Marked tolerance: need for markedly increased amounts of the substance in order to achieve intoxication or desired effect, or markedly diminished effect with continued use of the same amount</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Characteristic withdrawal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Substance often taken to relieve or avoid withdrawal symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Some symptoms of the disturbance have persisted for at least one month, or have occurred repeatedly over the longer period of time</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Substance Abuse/Dependence and Alcohol Use Disorder Criteria, continued

<table>
<thead>
<tr>
<th>DSM-IV-TR</th>
<th>DSM 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B.</strong> As manifested by 3 (or more) of the following, occurring at any time in the same 12 month period:</td>
<td>7. Important social, or occupational, or recreational activities are given up or reduced because of alcohol use</td>
</tr>
<tr>
<td>1. Tolerance: need for increased amounts of substance to achieve intoxication or desired effect or diminished effect with continued use of same amount of substance</td>
<td>8. Recurrent alcohol use in situations in which it is physically hazardous</td>
</tr>
<tr>
<td>2. Withdrawal: characteristic withdrawal syndrome for the particular substance (e.g., symptoms are unique to each substance) or the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms</td>
<td>9. Alcohol use is continued despite knowledge of having a persistent or recurrent psychological or psychological problem that is likely to have been caused or exacerbated by alcohol</td>
</tr>
<tr>
<td>3. Substance taken in larger amounts or over longer time than intended</td>
<td>10. Tolerance, as defined by either of the following:</td>
</tr>
<tr>
<td>4. Persistent desire or unsuccessful efforts to cut down and control substance use</td>
<td>a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect</td>
</tr>
<tr>
<td>5. Great deal of time spent on substance use (includes obtaining, using, and recovering)</td>
<td>b. A markedly diminished effect with continued use of the same amount of alcohol</td>
</tr>
<tr>
<td>6. Important activities (social, occupational, recreational) are given up/reduced due to substance use</td>
<td>11. Withdrawal, as manifested by either of the following:</td>
</tr>
<tr>
<td>7. Substance use continued despite knowledge of persistent or recurrent psychological or psychological problem likely related to substance use</td>
<td>a. The characteristic withdrawal syndrome for alcohol (refer to Criteria A or B of the criteria set for alcohol withdrawal)</td>
</tr>
<tr>
<td>b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms</td>
<td></td>
</tr>
</tbody>
</table>

**Specify if:**

**In early remission:** After full criteria for alcohol use disorder were previously met, none of the criteria for alcohol use disorder have been met for at least 3 months but for less than 12 months (with the exception that Criterion A4, “Craving, or a strong desire or urge to use alcohol,” may be met)

**In sustained remission:** After full criteria for alcohol use disorder were previously met, none of the criteria for alcohol use disorder have been met at any time during a period of 12 months or longer (with the exception that Criterion A4, “Craving, or a strong desire or urge to use alcohol,” may be met)

**Specify if:**

**In a controlled environment:** This additional specifier is used if the individual is in an environment where access to alcohol is restricted

**Specify current severity:**

**Mild:** Few, if any, symptoms in excess of those required to make the diagnosis, and the symptoms result in no more than mild impairment in occupational functioning or in usual social activities or relationships with others

**Moderate:** Symptoms or functional impairment between “mild” and “severe”

**Severe:** Many symptoms in excess of those required to make the diagnosis, and they symptoms markedly interfere with occupational functioning or with usual social activities or relationships with others

**In Partial Remission:** During the past six months, some use of the substance and some symptoms of dependence

**In Full Remission:** During the past six months, either no use of the substance, or use of the substance and no symptoms of dependence

**Specify current severity:**

**Mild:** Presence of 2-3 symptoms

**Moderate:** Presence of 4-5 symptoms

**Severe:** Presence of 6 or more symptoms
### Major Depressive Disorder Criteria

**DSM-III-R, DSM-IV-TR and DSM-5**

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear or dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. The episode is not attributable to the physiological effects of a substance or to another medical condition

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorders

E. There has never been a manic episode or a hypomanic episode

### DSM-III-R and DSM-IV-TR

<table>
<thead>
<tr>
<th>Specify if:</th>
<th>DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Specify:</td>
</tr>
<tr>
<td>Moderate</td>
<td>With anxious distress</td>
</tr>
<tr>
<td>Severe, without Psychotic Features</td>
<td>With mixed features</td>
</tr>
<tr>
<td>With Psychotic Features</td>
<td>With melancholic features</td>
</tr>
<tr>
<td>- Mood-congruent psychotic features</td>
<td>With atypical features</td>
</tr>
<tr>
<td>- Mood-incongruent psychotic features</td>
<td>With mood-congruent psychotic features</td>
</tr>
<tr>
<td>In Partial Remission</td>
<td>With mood-incongruent psychotic features</td>
</tr>
<tr>
<td>In Full Remission</td>
<td>With catatonia</td>
</tr>
<tr>
<td>Unspecified</td>
<td>With peripartum onset</td>
</tr>
</tbody>
</table>

### DSM-5

<table>
<thead>
<tr>
<th>Specify if:</th>
</tr>
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<tbody>
<tr>
<td>With seasonal pattern</td>
</tr>
</tbody>
</table>
## Appendix B: Assessment Rating Scales\(^{14, 35, 36}\)

<table>
<thead>
<tr>
<th>Rating Scale</th>
<th>Description</th>
</tr>
</thead>
</table>
| Beck Depression Inventory-II              | • Copyrighted self-rating scale designed to measure the severity of depressive symptoms that the individual is currently experiencing  
• 21 items scored from 0 to 3 (higher ratings indicated increased severity)  
• Total score 0 to 13 – minimal depression; 14 to 19 – mild depression; 20 to 28 – moderate depression; 29 to 63 – severe depression |
| Montgomery-Asberg Depression Rating Scale (MADRS) | • Common clinician-rating scale designed to measure the degree of severity of depressive symptoms and the change in symptom severity during the treatment of depression  
• 10 items scored from 0 to 6 (higher ratings indicate increased severity): apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, suicidal thoughts  
• Total score 0 to 6 – no symptoms; 7 to 19 – mild depression; 20 to 34 – moderate depression; >34 – severe depression |
| Alcohol Use Disorders Identification Test (AUDIT) | • Developed by the World Health Organization (WHO) as a simple method to screen for excessive drinking and identify people at risk of alcohol problems  
• 10 items scored from 0 to 4 (higher ratings indicate increased severity)  
• A total score of 8 or more indicates harmful drinking behavior |
References