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Could SSRIs Lead To Increased Alcohol Consumption In Some Populations?

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ABSTRACT

Studies with both rats and humans show that Selective Serotonin Reuptake Inhibitors (SSRIs) lead to a short term reduction in alcohol consumption (AC); however, AC returns to at least baseline levels at the end of one week in humans. The SSRI fluoxetine (Prozac) shows significantly better results than placebo in reducing both AC and depression in Alcohol Dependent subjects with comorbid severe Major Depressive Disorder. However, SSRIs are not better than and may be worse than placebo in reducing AC in individuals who do not suffer from severe Major Depressive Disorder. In subjects who lack major depressive disorder it appears that SSRIs significantly interfere with the impact of psychosocial therapy on the AC of both women and individuals with Early Onset Alcohol Use Disorder (AUD). I. e. women and individuals with Early Onset AUD who received an SSRI and psychosocial therapy for drinking showed significantly less reduction in AC than did subjects who received a placebo and psychosocial therapy. This suggests that SSRIs might potentially increase AC in women and in individuals with Early Onset AUD who do not receive any psychosocial therapy for their drinking. Further research is called for to confirm this hypothesis.

Introduction

Early research with both rats and humans suggested that the serotonergic system is involved in Alcohol Use Disorders (AUDs). A number of researchers found serotonergic deficiencies in the brains of alcohol preferring rats (Rezvani, Overstreet & Janowsky, 1990; Gongwer, Murphy, McBride, Lumeng & Li, 1989; McBride, Bodart, Lumeng & Li, 1995; Korpi, Päivärinta, Abi-Dargham, Honkanen, Laruelle, Tuominen & Hilakivi, 1992). Meert (1993) found that Selective Serotonin Reuptake Inhibitors (SSRIs) reduce Alcohol Consumption (AC) in rats in a short term (4 day) study. Other researchers have found similar effects in rats.

Several researchers also found that SSRIs led to short term reduction of AC in humans as well (Amit, Brown, Sutherland, Rockman, Gill & Selvaggi, 1985; Naranjo, Sellers, Roach, Woodley, Sanchez-Craig, & Sykora, 1984; Naranjo, Sellers, Sullivan, Woodley, Kadlec & Sykora, 1987; Naranjo, Sullivan, Kadlec, Woodley-Remus, Kennedy. & Sellers, 1989; Naranjo, Kadlec, Sanhueza, Woodley-Remus & Sellers,1990). However, long term studies do not demonstrate that SSRIs are more effective than a placebo in reducing AC in general populations of individuals with AUDs (Gorelick & Paredes, 1992; Kabel & Petty, 1996; Kranzler, Burleson, Korner, Del Boca, Bohn, Brown & Liebowitz, 1995). Some studies suggest that SSRIs may actually exacerbate AUDs in certain populations--namely women and individuals with early onset AUD (Kranzler, Burleson, Brown & Babor, 1996; Naranjo, Bremner, Lanctot, 1995; Pettinati, Volpicelli, Kranzler, Luck, Rukstalis, Cnaan, 2000).

SSRIs are, however, more effective than placebo in reducing both alcohol consumption and symptoms of depression in Alcohol Dependent subjects with comorbid severe Major Depressive Disorder (MDD) (Cornelius, Salloum, Ehler, Jarrett, Cornelius, Perel, Thase & Black, 1997).

The present paper will review the results of seven studies on the effect of SSRIs on AC in humans and will make a suggestion for further experimental research which could help to clarify some still unanswered questions about the utility and safety of SSRIs in various populations of individuals with AUD or recreational drinkers. Data from these seven studies are tabulated in Table 1.

Table 1) Summary of Human Studies on SSRIs and Alcohol Consumption (AC)

Study	Gorelick et al 1992	Kabel et al 1996	Kranzler et al 1995	Kranzler et al 1996	Naranjo et al 1995	Pettinati et al 2000	Cornelius et al 1997
Duration	4 weeks	4 + 12 weeks	12 weeks	12 weeks	12 weeks	14 weeks	2 + 10 weeks
Subjects Total	N=20	N=28	N=101	N=95	N=62	N=100	N=51
Male	N=20	N=28	N=81	N=76	N=35	N=52	N=26
Female	N=0	N=0	N=20	N=19	N=27	N=48	N=25
Sex ratio	100% M	100% M	80% M	80% M	56% M	52% M	51% M
Medication	fluoxetine (Prozac)	fluoxetine (Prozac)	fluoxetine (Prozac)	fluoxetine (Prozac)	citalopram (Celexa)	Sertraline (Zoloft)	fluoxetine (Prozac)
Dosage	80 mg/day	60 mg/day	60 mg/day	60 mg/day	40 mg/day	200 mg/day	25 mg/day 40 max
Medication group	N=10	N=15	N=51	N=46	N=31	N=50	N=25
Placebo group	N=10	N=13	N=50	N=49	N=31	N=50	N=26
Alcohol dependency	severe	severe	mild to moderate	mild to moderate	mild to moderate	mild to moderate	severe
drinks/week @ baseline	148	130	50	50	43	46	N/A
DSM Alc Dp Criteria	Met	Met	Met	Met	Met	Met	5.7± 1.7 of 9
Early Onset Subtype	N/A	N/A	N/A	N=35	N/A	N=45	N/A
Late Onset Subtype	N/A	N/A	N/A	N=60	N/A	N=55	N/A
Current MDD	Non-depressed	Non-depressed	14%	N/A	Non-depressed	53% (lifetime)	100%
BDI Pre-Tx	N/A	N/A	7.0	N/A	5.2	N/A	27.2 16 dtx
HAM-D-24 Pre-Tx	N/A	N/A	N/A	N/A	N/A	9.5	33.1 18.6 dtx

Table 1 Continued							
HRSD Pre-Tx	2.3	N/A	5.9	N/A	N/A	N/A	N/A
DSM MDD criteria	N/A	N/A	N/A	???	N/A	N/A	6.8±1.1 of 9
Condition	Locked Ward	4 wk ip 12 wk op	Outpatient	Outpatient	Outpatient	Outpatient	2 wk ip 10 wk op
Study	Gorelick et al 1992	Kabel et al 1996	Kranzler et al 1995	Kranzler et al 1996	Naranjo et al 1995	Pettinati et al 2000	Cornelius et al 1997
Tx Goal	N/A	Abstinence	Abstinence	Abstinence	Moderation or abstinence	Abstinence	Abstinence
Treatment Seeking	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Psychosocial Tx	None	Varied	Coping skills, relapse prevention	Coping skills, relapse prevention	Guidelines for Sensible Drinking	12 step facilita-tion weekly	Weekly session w/ therapist & psychiatrist & AA
Short term drink reduction	Yes	N/A	N/A	N/A	Yes	N/A	N/A
Long term drink reduction	No	No	No	No	No	No	Yes
Sex × MedGroup interaction	N/A	N/A	N/A	N/A	Yes	N/A	N/A
Subtype × MedGroup interaction	N/A	N/A	N/A	Yes	N/A	Yes	N/A

Gorelick and Paredes (1992)
This was a 4 week placebo controlled double blind study of fluoxetine (Prozac) conducted on a locked ward with 20 non-depressed, severely Alcohol Dependent males. Subjects were given no psychosocial treatment during the course of the experiment. Subjects were allowed access to alcohol in a fixed interval drinking decision (FIDD) paradigm. Baseline was 148 standard drinks[1] per week. Subjects showed a significant decrease in AC compared to baseline in first week ($p = 0.02$), but no significant difference from baseline in subsequent weeks. There were no significant changes in Hamilton depression scores.

Kabel and Petty (1996)
This was a 16 week placebo controlled double blind study of fluoxetine (Prozac) in conjunction with psychosocial therapy. Subjects were 28 non-depressed, severely alcohol Dependent males. Baseline was 130 standard drinks per week. Treatment was 4 weeks inpatient followed by 12 weeks outpatient.

The fluoxetine treated group showed a trend to relapse sooner than the placebo treated group. This trend did not attain statistical significance. It would be interesting to see if a larger sample size would show a statistically significant effect. There were no statistically significant difference between the fluoxetine treated group and the placebo group.

Kranzler, Burleson, Korner, Del Boca, Bohn, Brown and Liebowitz (1995)
This was a 12 week placebo controlled double blind outpatient study of fluoxetine (Prozac) in conjunction with psychosocial therapy with 101 non-depressed subjects with mild to moderate alcoholic dependence. Baseline was 50 standard drinks per week. Subjects were 80% male.

An effect of Gender × Time attained statistical significance ($p = 0.01$). However the effect of Gender × Time × Medication Group did not attain statistical significance. In other words this study did not show that fluoxetine was significantly better or significantly worse than placebo for women in the study. That this failed to attain statistical significance might be due to the underrepresentation of women in the study. No statistically significant differences between the medication group and the placebo group were found.

Kranzler, Burleson, Brown and Babor. (1996):
This was a post hoc reanalysis of data from Kranzler et al (1995). Subjects from Kranzler (1995) were classified as Early Onset and Late Onset subtypes. The Early Onset subtype was defined as consisting of subjects who began drinking at a younger age and who had more severe consequences from their drinking. 6 subjects were eliminated because there was insufficient evidence to classify them.

Numbers of subjects were as follows:

- Late Onset: ($n = 60$); male ($n = 47$), female ($n = 13$); fluoxetine ($n = 28$), placebo ($n = 32$)
- Early Onset: ($n = 35$); male ($n = 29$), female ($n = 6$); fluoxetine ($n = 18$), placebo ($n = 17$)

[1] Throughout this paper a standard drink is defined as consisting of 0.5 oz of ethanol.

Kranzler et al (1996) used three measures to determine differences in AC of subjects: number of drinking days, drinks per drinking day, and elevation of GGTP enzyme levels. Number of drinking days and drinks per day were determined pre-treatment and post-treatment by using a Time-Line Follow-Back questionnaire (Sobell, Maisto, Sobell, Cooper, Cooper & Sanders, 1980) corroborated by a collateral informant chosen by the subject. GGTP elevation is directly correlated with alcohol consumption and was determined pre-treatment and post-treatment via blood test.

Univariate analysis of the reduction in GGTP liver enzyme elevation showed fluoxetine to be significantly worse than placebo in subjects with Early Onset AUD ($p = 0.022$). This suggests that subjects with Early Onset AUD under the fluoxetine condition reduced their drinking by significantly less than did those under the placebo condition. This is shown graphically in Figure 1.

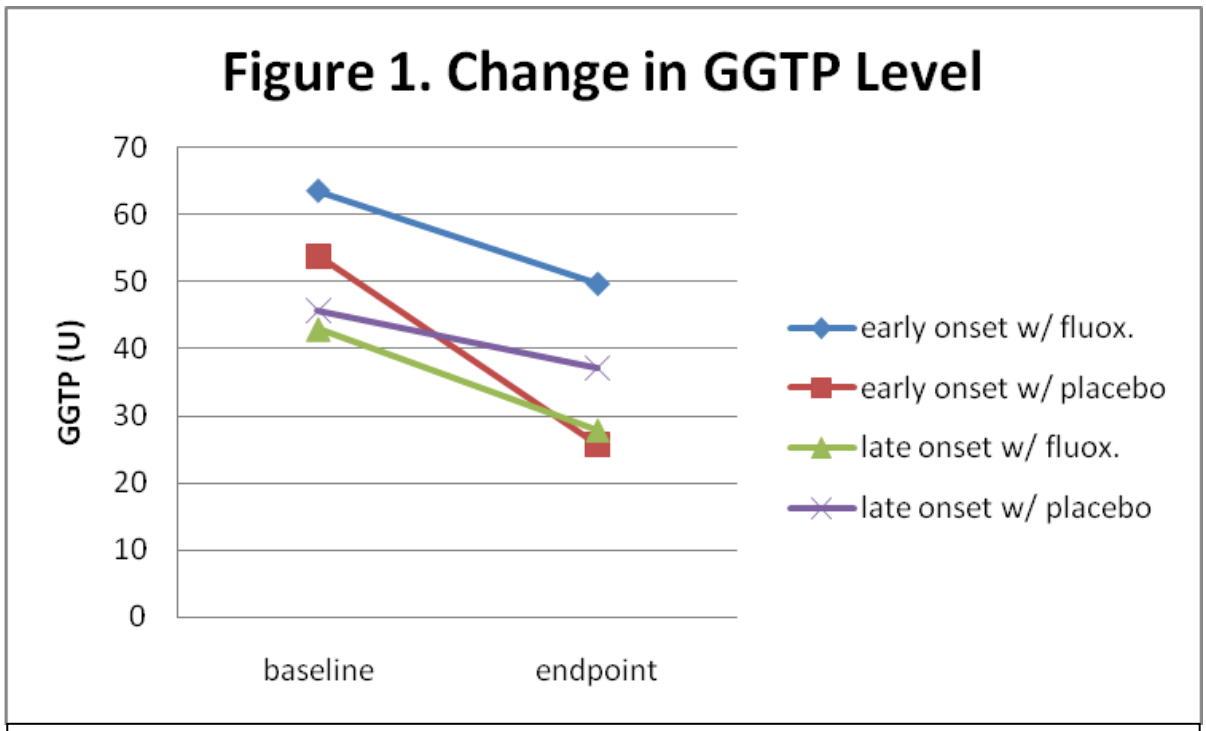

Figure 1. Subjects with Early Onset AUD showed significantly worse outcomes for GGTP liver enzyme under the fluoxetine condition than under the placebo condition. ($p = 0.022$). Adapted from Kranzler et al (1996).

Univariate analyses of the number of drinks per day and the number of drinking days did not attain statistical significance, however, multivariate analysis on three drinking measures taken together (number of drinking days, drinks per drinking day, GGTP) showed fluoxetine to be significantly worse than placebo in subjects with Early Onset AUD ($p = 0.031$). This may be due to the fact that the Time-Line Follow-Back questionnaire is not accurate enough to show statistically significant differences.

No statistically significant sex effect for the Early Onset subtype was found but the sample size was small with only 6 females in the Early Onset subtype..

The subjects in this study were given both medication treatment (fluoxetine or placebo) and psychosocial Alcohol Dependency treatment (Coping Skills and Relapse Prevention) with the goal of reducing or eliminating their alcohol consumption. Since the fluoxetine treated Early Onset subjects fared worse in this study, we are led to ask whether fluoxetine might actually increase AC in Early Onset subjects receiving no adjunct psychosocial treatment.

Naranjo, Bremner and Lanctot (1995)
This was a 12 week placebo controlled double blind outpatient study of citalopram (Celexa) in conjunction with psychosocial therapy with 62 non-depressed subjects with mild to moderate alcoholic dependence. Baseline was 43 standard drinks per week. Subjects were 56% male.

Psychosocial treatment consisted of a brief intervention and the pamphlet: Guidelines for Sensible Drinking.

Subjects under the citalopram condition did not show significantly better outcomes than under the placebo condition for any measures. However, males did significantly better than females ($p < 0.05$) under the citalopram condition on the measure of decrease in drinks per day. This implies that females did significantly better under the placebo condition and significantly worse under the citalopram condition than did males for this measure.

The decrease in AC from baseline which resulted from citalopram combined with psychosocial therapy was an average of 44% (± 5.3) among the males, and 25.7% (± 6.3) among the females, The average decrease from baseline in the placebo condition was 39.9% (± 5.8) for females and 38.0% (± 3.6) for males. This is illustrated graphically in Figure 2.

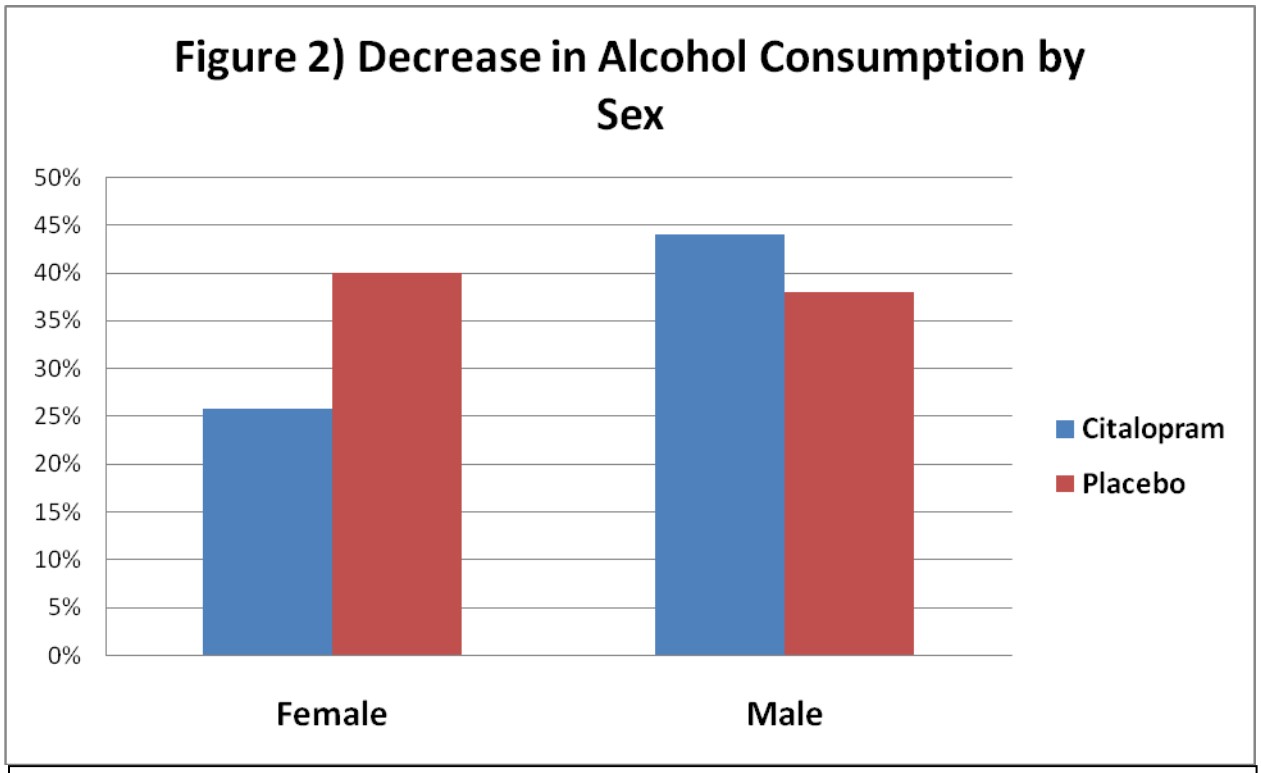

Figure 2. Males did significantly better than females ($p < 0.05$) under the citalopram condition on the measure of decrease in drinks per day. Adapted from Naranjo et al (1995).

Studies of the psychosocial intervention used in the absence of medication showed better response by females than males, This leads us to the hypothesis that females might actually increase AC when given citalopram in the absence of psychosocial therapy.

Pettinati, Volpicelli, Kranzler, Luck, Rukstalis and Cnaan (2000)
This was a 14 week placebo controlled double blind outpatient study of sertraline (Zoloft) in conjunction with psychosocial therapy with 100 subjects with mild to moderate alcoholic dependence. Baseline was 46 standard drinks per week. Subjects were 52% male. 55% of subjects had Late Onset AUD, 45% hade Early Onset AUD. 53% of subjects met DSM criteria for lifetime Major Depressive Disorder.

Psychosocial treatment consisted of weekly Twelve Step Facilitation therapy via a manual.

Late Onset subjects had significantly fewer drinking days under the sertraline condition than under the placebo condition ($p = 0.01$). This trend was reversed in Early Onset subjects although this did not reach statistical significance ($p = 0.46$).. This is illustrated in Figure 3. Medication Condition $\times$ Subtype ($p = 0.05$).

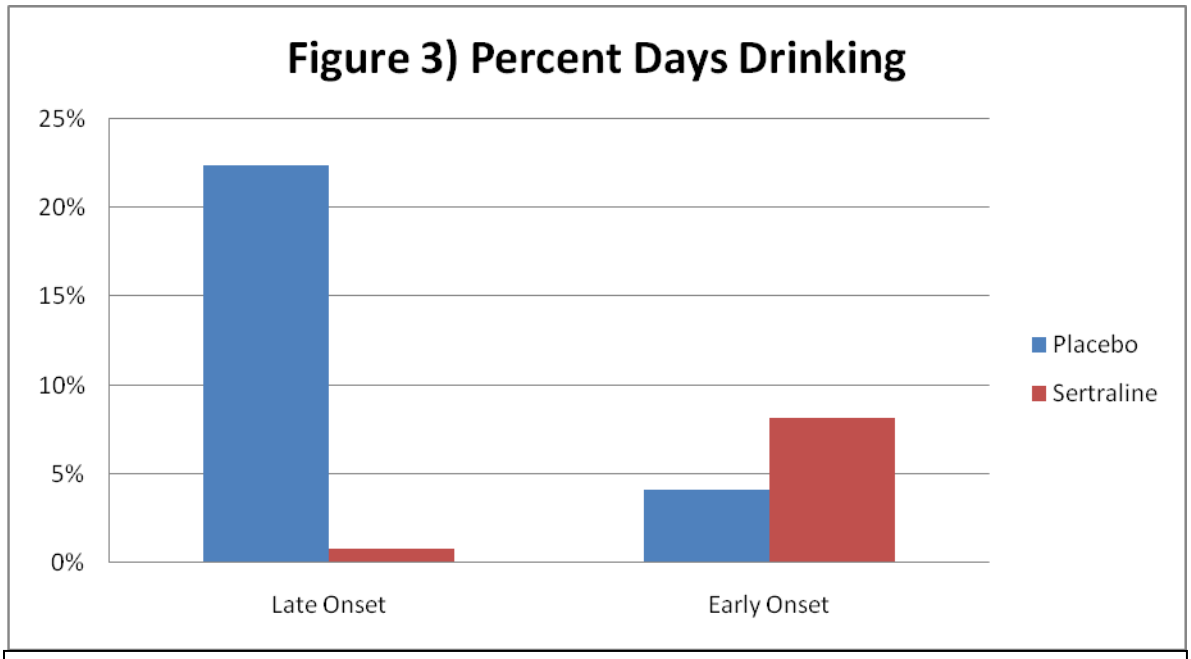

Figure 3. Late Onset subjects under the sertraline condition had significantly fewer drinking days than did subjects under the other conditions ($p = 0.01$). Adapted from Pettinati et al (2000).

A significantly greater number of Late Onset subjects maintained continuous abstinence under the medication condition than under the placebo condition (53.3% vs. 16.0%; $p = 0.004$). This trend was reversed in Early Onset subjects. More Early Onset subjects maintained continuous abstinence under the placebo condition than under the medication condition but this trend did not attain statistical significance (10.0% vs. 24.0%; $p = 0.22$). This is illustrated graphically in Figure 4. Medication Condition × Subtype ($p = 0.009$).

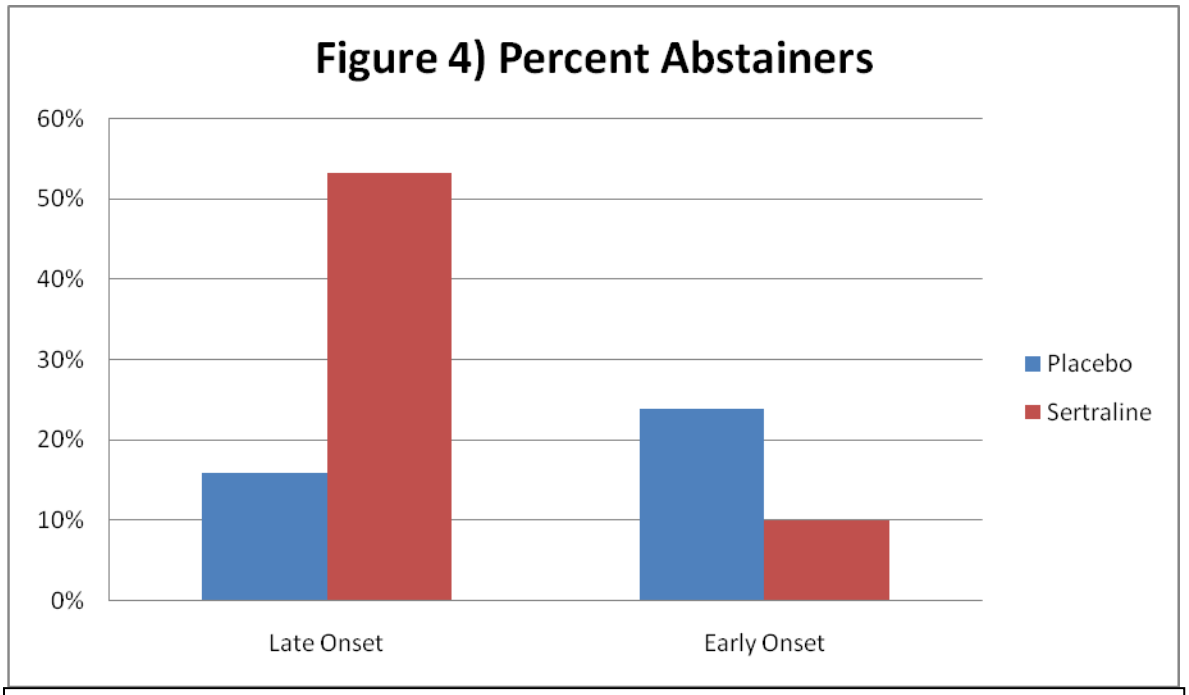

Figure 4. A significantly larger percent of Late Onset subjects under the sertraline condition maintained continuous abstinence than did subjects under the other conditions ($p = 0.004$). Adapted from Pettinati et al (2000).

In contrast to Kranzler's results using fluoxetine, Pettinati's results with sertraline show Late Onset subtypes doing better under the medication condition than under the placebo condition, whereas the Early Onset Subtype does no better or worse under the medication condition than under the placebo condition.

There may be a confound in Pettinati's data because Pettinati used Hamilton Depression scores as a factor in determining alcoholic subtype (Late Onset vs. Early Onset). Hence, the fact that Early Onset Alcoholics did not do worse under the medication condition than under the placebo condition (unlike Kranzler) may have been due to the fact that they were more depressed than the subjects in the Kranzler study and hence were reacting like the subjects in the Cornelius study. In other words the determining factor may have been the degree of depression rather than the fact that sertraline rather than fluoxetine was the medication.

Subjects in Kranzler's study showed a 14% prevalence of current depression, whereas subjects in Pettinati's study showed a 53% lifetime prevalence of depression. The Hamilton depression score across all subjects in Kranzler's study was HRSD = 5.9. In Pettinati HAM-D-24 = 9.5 across all subjects.

Cornelius, Salloum, Ehler, Jarrett, Cornelius, Perel, Thase and Black (1997)
This was a 12 week placebo controlled double blind study of fluoxetine (Prozac) in conjunction with psychosocial therapy with 51 subjects with severe Alcohol Dependence and comorbid severe Major Depressive Disorder (MDD). Subjects met 5.7± 1.7 of 9 DSM-III-R Criteria for Alcohol Dependence and 6.8±1.1 of 9 DSM-III-R criteria for MDD. Subjects were 51% male. 90% reported suicidal ideations

in the week before hospitalization, 35% made a suicide attempt in the week before admission to the hospital and 61% had made a suicide attempt in their lifetime. Treatment was 2 weeks inpatient, 10 weeks outpatient.

Psychosocial treatment consisted of weekly sessions with a therapist and with a psychiatrist and optional AA attendance.

Fluoxetine in conjunction with psychosocial therapy led to significantly greater reductions in both depressive symptoms and drinking than did psychosocial therapy in conjunction with placebo. However, contrary to expectations the reductions in depression were not correlated with reductions in drinking in the fluoxetine treated group. They were, however, positively correlated in the placebo group. This seems to suggest that depression which is reduced by psychosocial therapy has a correlation with reduced drinking but that reduction in depression and reduction in drinking in response to the fluoxetine are independent of each other. Further research is needed on this topic.

Data on drinking outcomes are tabulated in Table 2 and data on depression outcomes are tabulated in Table 3. Figure 5 shows the reduction in Hamilton Depression scores and Figures 6 and 7 show the reductions in drinking outcomes.

Table 2) Drinking outcomes between groups		
Total alcohol consumption	Significantly better	$p < 0.03$
Cumulative number of drinking days	Significantly better	$p < 0.05$
Number of drinks per drinking day	Significantly better	$p < 0.05$
Number of heavy drinking days	Significantly better	$p = 0.04$
Weeks to first heavy drinking day	Significantly better	$p < 0.02$
Percent of totally abstinent individuals	Not significant	$p = 0.27$
AA attendance	Not significant	$P = 0.92$

Table 3) Depression outcomes between groups		
HAM-D-24	Significantly better	$p < 0.05$
BDI	Not significant	$p = 0.17$

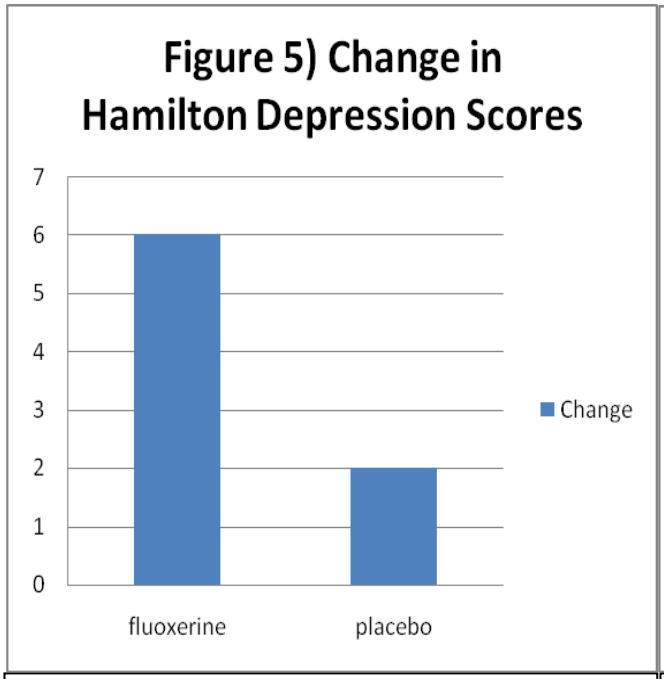

Figure 5. The HAM-D-24 was adminstered at the beginning and conclusion of fluoxetine treatment. Data is from Cornelius et al 1997.

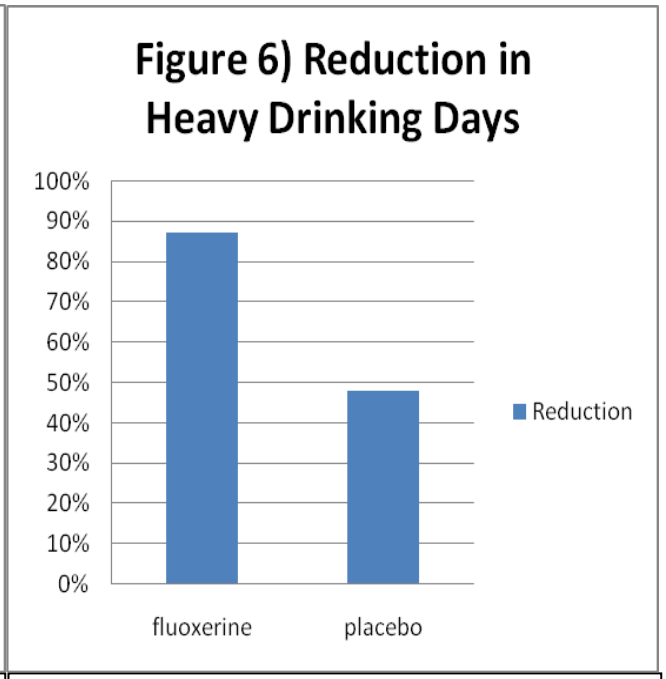

Figure 6. The number of heavy drinking days was measured over the 12 week period of fluoxetine treatment and compared with baseline. Data is from Cornelius et al 1997.

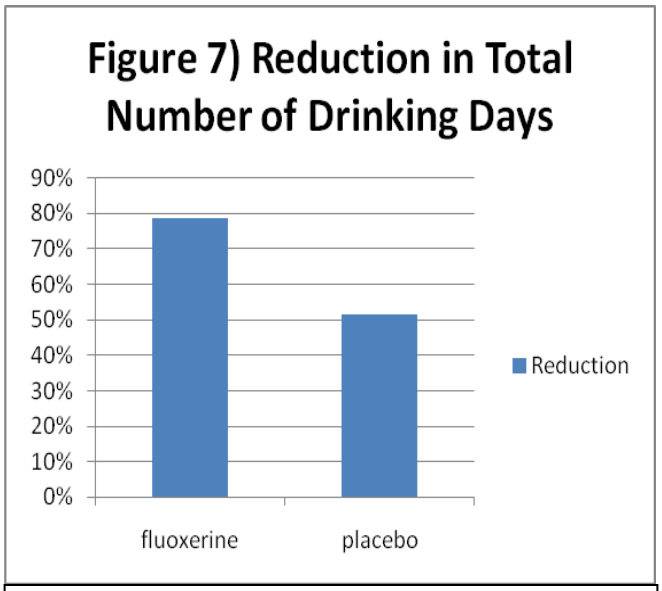

Figure 7. The number of drinking days was measured over the 12 week period of fluoxetine treatment and compared with baseline. Data is from Cornelius et al 1997.

Conclusion

Research demonstrates that SSRI are of use in treating individuals with Alcohol Use Disorder only when there is severe comorbid Major Depressive Disorder and severe Alcohol Dependence Disorder (Cornelius et al, 1997). SSRIs are not useful in treating Alcohol Use Disorders in other populations (Gorelick & Paredes, 1992; Kabel & Petty, 1996; Kranzler et al, 1995). Moreover, data from Kranzler et al (1996) suggest a possibility that SSRIs may actually exacerbate AUDs in early onset alcoholics; data from Naranjo et al (1995) suggest the possibility that SSRIs may exacerbate AUDs in women. It is unfortunate that prescribers and the general public seem generally uninformed or even misinformed about the use of SSRIs for AUDs as is evidenced by this quote from the Alcoholism page of the web site of the University of Maryland Medical Center "Newer antidepressants such as selective serotonin reuptake inhibitors (SSRIs) are proving to be very useful complements to AA or counseling sessions". Obrien and McKay's (2002) rather extensive literature review of pharmacological treatments for SUDs mentions only positive outcomes from use of SSRIs for AUDs and fails to mention negative ones. Johnson's (2004) literature review is more balanced in that it mentions some negative results; however, a number of other literature reviews covering the topic of the use of SSRIs for AUDs also fail to mention negative outcomes.

Therefore I propose that experimental research be carried out to determine whether SSRIs exacerbate AUDs and lead to an increase in Alcohol Consumption in women and in early onset alcoholics in the absence of psychosocial counseling. If this should be the case then I propose that the FDA labeling of these SSRIs be updated to include this information.

In the mean time I would urge prescribers to use caution when prescribing SSRIs to people who drink alcohol and to pay attention if their patients complain that SSRIs are causing them to crave alcohol or to drink more.

In summary it appears that three factors are involved in how SSRIs affect Alcohol Consumption: sex, depression, and alcoholic subtype. SSRIs appear to lower Alcohol Consumption in individuals suffering from severe Major Depressive Disorder but may increase Alcohol Consumption in women or in Early Onset Alcohol Dependents. I propose the following experiments to confirm these hypotheses.

Research Proposal

Experiment 1)

Hypothesis: SSRIs affect AC significantly differently in female rats than male rats.

A search of the abstracts of the PubMed database shows that all rat studies of the effect of SSRIs on AC either state that they have been done on male rats, or simply on rats. No rat study appears to have been done to determine if sex is a factor in the effect of SSRIs on AC.

Subjects will be 800 alcohol preferring rats--400 male rats and 400 female rats. Half the subjects of each sex will be given access to alcohol ad libitum; half will have access one hour per day after a period of alcohol habituation (the "happy hour" condition).

After two weeks to establish a baseline, half the subjects in each category shall be given fluoxetine and half a placebo. The hypothesis is that there will be a statistically significant difference in AC based on Sex × Medication Group in both the ad libitum condition and the "happy hour" condition.

Experiment 2)

Hypothesis: SSRIs affect AC significantly differently in female humans than male humans.

Recruit 400 female heavy drinkers (> 30 drinks/week) and 400 male heavy drinkers (> 40 drinks/week) via advertisements as research subjects[2].

Subjects interested in reducing their drinking will be excluded from the study. Subjects will be told that we are testing side effects of a new medication. Subjects will track mood, eating, alcohol intake, sugar intake, weight change, nausea, etc. Subjects will not know that they are taking an antidepressant nor that we are interested primarily in AC.

Recruits complete Becks Depression Inventory and Hamilton's Depression Scale. Recruits also complete a questionnaire about eating habits, drinking habits, PMS, sweet consumption, headache, and nausea.

2 weeks of self report to establish baseline - includes teaching how to measure a standard drink

A 12 week study of fluoxetine (Prozac) vs placebo will follow`; half of the male subjects and half of the female subjects will receive fluoxetine, the other half of each placebo.

Evaluate if there is a statistically significant effect of Sex × Medication Group on AC.

Experiment 3)

Hypothesis: in the absence of psychosocial treatment fluoxetine causes an increase in AC over baseline in subjects with Early Onset AUD.

A locked ward study with a design similar to that of Gorelick and Paredes (1992) where subjects have access to up to one liter of 80 proof vodka per day in a fixed interval drinking decision (FIDD) paradigm. Subjects would consist of 400 non-depressed Alcohol Dependents. 200 would be Early Onset Subtype and 200 would be Late Onset Subtype. After a two week period where all receive placebo and where a baseline is established, the medication condition with fluoxetine will begin. Half the subjects in each subtype will be administered 60 mg/day of fluoxetine and half placebo. The hypothesis is that subjects in the Early Onset Subtype who receive fluoxetine will increase their alcohol consumption over the long term whereas the others will not. Tx will last for ten weeks after baseline is established.

[2] Heavy drinking is defined differently for male than for females because females attain higher BACs for the same amount of ethanol due to less alcohol dehydrogenase being present in the stomachs of females.

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