Effect of a brain-penetrant selective estrogen receptor degrader (SERD) on binge drinking in female mice

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Abstract

Background: Greater circulating levels of the steroid hormone 17β-estradiol (E2) are associated with higher levels of binge drinking in women. In female mice, estrogen receptors in the ventral tegmental area, a dopaminergic region of the brain involved in the motivation to consume ethanol, regulate binge-like ethanol intake. We recently developed a brain-penetrant selective estrogen receptor degrader (SERD), YL3-122, that could be used to test the behavioral role of brain estrogen receptors. We hypothesized that treating female mice with this compound would reduce binge-like ethanol drinking.

Methods: Female C57BL/6J mice were treated systemically with YL3-122 and a related SERD with low brain penetrance, XR5-27, and tested for binge-like ethanol consumption in the drinking in the dark (DID) test. Mice were also tested for sucrose and water intake and blood ethanol clearance after treatment with the SERDs. Finally, the effect of ethanol exposure on Esr1 gene expression was measured in the ventral tegmental area (VTA), prefrontal cortex (PFC), and ventral hippocampus (vHPC) of male and female mice by quantitative real-time PCR after 4 DID sessions.

Results: YL3-122 reduced ethanol consumption when mice were in diestrus but not estrus. YL3-122 also decreased sucrose consumption but did not alter water intake or blood ethanol clearance. XR5-27 did not affect any of these measures. Binge-like ethanol drinking resulted in increased Esr1 transcript in the VTA of both sexes, male vHPC, and female PFC.

Conclusions: These results indicate that SERD treatment can decrease binge-like ethanol drinking in female mice. Thus, it could be a novel strategy to reduce binge drinking in women, with the caveat that effectiveness may depend on menstrual cycle phase. In addition, Esr1 transcript is increased by binge ethanol exposure in both sexes but in a brain region-specific manner.

KEYWORDS
binge drinking, estrogen, estrogen receptor, SERD, sex differences

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INTRODUCTION

Women are drinking more alcohol now than in previous decades, with the prevalence of high-risk, or binge, drinking by women increasing by 57.9% from 2002 to 2013 (Grant et al., 2017). Binge drinking is defined by the National Institute on Alcohol Abuse and Alcoholism as drinking enough alcohol to reach a blood alcohol concentration of 0.08% or greater, which typically occurs in women after consuming 4 drinks in approximately 2 h. Binge drinking is problematic because it increases the risk of developing alcohol use disorder (AUD) and has negative health effects on the cardiovascular system, brain, and liver, particularly in women (Agabio et al., 2016; Szabo, 2018). In addition, binge drinking increases the risk of breast cancer (White et al., 2017).

The underlying neurobiological mechanisms that contribute to high-risk drinking may differ between men and women. For example, estrogens, which are produced by the ovaries and fluctuate throughout the menstrual cycle, have been associated with higher levels of drinking in women (Martel et al., 2017; Muti et al., 1998). Animal experiments have demonstrated a role for the most abundant circulating form of estrogen, 17β-estradiol (E2), in promoting high levels of alcohol intake (Finn, 2020). Specifically, female mice consume more EtOH than males in a binge drinking procedure (Rhodes et al., 2005; Satta et al., 2018), ovary removal reduces binge-like EtOH intake to levels comparable to those seen in male mice, and supplementing ovariectomized mice with E2 restores high levels of EtOH intake (Satta et al., 2018). E2 activates estrogen receptors (ERα, ERβ, and GPR30 or GPER) that are expressed throughout the brain. Notably, reducing the expression of ERα and to a lesser extent, ERβ, in the ventral tegmental area (VTA), a dopaminergic region of the brain involved in binge alcohol consumption, results in decreased binge-like alcohol intake in female but not in male mice (Vandegrift et al., 2020). Together, these studies indicate sexually dimorphic roles for estrogen receptors in the brain on excessive alcohol consumption and suggest that inhibiting brain estrogen receptors could be a useful pharmacotherapeutic strategy in women to reduce binge drinking.

Estrogen receptors are targets of drugs called selective estrogen receptor modulators (SERMs) and selective estrogen receptor degraders (SERDs). The SERMs, such as tamoxifen and raloxifene, act as agonists or antagonists of estrogen receptors depending on the tissue type (Martinkovich et al., 2014), whereas the SERDs such as fulvestrant (ICI 182,780) are estrogen receptor antagonists that induce proteasomal degradation of estrogen receptors (Osborne et al., 2004). Given that SERMs have mixed agonist and antagonist properties and could conceivably either increase or decrease EtOH consumption in females, we reasoned that treatment with a SERD would be more likely to reduce binge EtOH drinking than a SERM. Fulvestrant, however, is problematic because it has poor pharmacokinetics and solubility and is administered via intramuscular injection. We previously developed an oral, brain bioavailable SERD, YL3-122 for use as treatment for brain metastases in estrogen receptor-positive breast cancer (Lu et al., 2019). Here, we tested this SERD for its effect on binge-like EtOH and sucrose drinking in the dark test and blood EtOH clearance in female mice to determine whether pharmacological inhibition of brain estrogen receptors could be a viable option for reducing binge drinking. We compared the effects of YL3-122 to an analogous orally bioavailable compound XRS-27 (Xiong et al., 2017), which has low brain penetrance, on binge-like drinking in the DID test. Finally, we measured the effect of binge levels of EtOH consumption on transcript levels of the gene encoding ERα (Esr1) in different brain regions in both female and male mice to begin to understand more generally the molecular mechanisms that may underlie sex differences in alcohol consumption. Our results suggest that brain bioavailable SERDs like YL3-122 can reduce binge-like EtOH intake in mice and warrant further consideration, as they have the potential to be novel pharmacotherapies for reducing high-risk drinking in women.

MATERIALS AND METHODS

Animals

Female and male C57BL/6J mice at the age of 8 weeks were purchased from the Jackson Laboratory and used for experiments when they were 10 weeks old. Mice were individually housed for drinking in the dark in a temperature- and humidity-controlled room with a reversed 12-h light/dark cycle (lights off at 10 AM), with food and water available ad libitum, except during the EtOH-only drinking session, when water was not provided during this limited time. For the EtOH clearance experiment, mice were group-housed in a standard 12-h light/dark cycle room (lights on at 6 AM). Mice were fed Teklad 7912 diet (Envigo). All procedures were approved by the UIC Animal Care Committee and animal care conformed with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Drinking in the dark (DID)

Drinking in the dark was conducted as described (Coles & Lasek, 2021; Hamada et al., 2021). Briefly, mice were given access to a sipper tube containing 20% EtOH or water, 3 h into the dark cycle for 2 h on the first 3 days, and 4 h on the 4th day. On the 4th day, volume of fluid consumed was measured at both 2 and 4 h. For the sucrose consumption test, a solution of 2% sucrose in water was provided for 2 h per day for 4 days. Eighteen female mice per group were used for measuring the effect of SERD treatment on EtOH intake, 12 female mice per group were used for measuring the effect of SERD treatment on sucrose intake, and six female mice per group were used for measuring the effect of SERD treatment on water intake. For measuring Esr1 gene expression by qPCR after DID with water or EtOH, both male and female mice (nine mice per sex per group) were used. Brain samples were those from previously...
published experiments (Coles & Lasek, 2021; Hamada et al., 2021). Drinking levels and BECs can be found in those studies. Mean BECs were confirmed to be above the intoxicating levels of 80 mg%.

**SERD administration**

XR5-27 was prepared at a concentration of 10 mg/ml in PEG 400, 0.5% carboxymethyl cellulose-Na, polyvinylpyrrolidone, and Tween-80 (9:90:0.5:0.5 in volume). YL3-122 was prepared at a concentration of 10 mg/ml in PEG 400 and 10% (2-hydroxypropyl)-β-cyclodextrin in water (1:9 in volume). The vehicle (VEH) control group received the solution used for YL3-122. Mice received 0.1 ml of VEH, YL3-122, or XR5-27 by oral gavage at a dose of ~50 mg/kg (based on average mouse weight of 20g), 5 h before the drinking session or i.p. EtOH administration for the EtOH clearance experiment. XR5-27 (Xiong et al., 2017) and YL3-122 (Lu et al., 2019) both have subnanomolar potency in cell-based reporter assays and cause degradation of ERα in mouse ovary and uterus after oral administration (Lu et al., 2019). YL3-122 has a bioavailability of 22%, a half-life of 4.5 h, and a brain/plasma ratio Cmax and AUClast of 1.54 and 1.26, respectively (Lu et al., 2019). XR5-27 with an acrylate moiety (Figure 1), on the contrary, only has a brain/plasma ratio Cmax and AUClast of 0.01 and 0.03, respectively (Xiong et al., 2017), serving as a low brain-penetrant control. Chemical structures of YL3-122 and XR5-27 are shown in Figure 1.

**Blood EtOH concentrations (BECs)**

A 20% EtOH in saline solution was injected i.p. at a dose of 2 g/kg and blood was collected from the tail vein 5, 30, 60, 90, 120, and 180 min after injection for measurement of BECs using an alcohol dehydrogenase-nicotinamide adenine dinucleotide enzymatic assay as previously described (Hilderbrand & Lasek, 2018). β-NAD and yeast ADH were purchased from Millipore Sigma.

**RNA isolation, reverse transcription, and quantitative real-time PCR (qPCR)**

Prefrontal cortex (PFC) and ventral hippocampus (vHPC) samples were the same as those reported in Hamada et al. (2021), and VTA samples were the same as those reported in Coles and Lasek (2021). Total RNA was extracted from brain samples using the RNeasy Mini kit (QIAGEN) according to the manufacturer's instructions and reverse transcribed using the High-Capacity cDNA Reverse Transcription kit (Thermo Fisher Scientific). qPCR was performed using SYBR green PCR master mix (Bio-Rad) with primers to mouse Esr1 (forward, 5′-CCTACTACCTGGAGAACGAGC-3′, reverse, 5′-GCACAGTAGCGAGTCTCCTT-3′). Relative mRNA levels were determined using the 2−ΔΔCt method using the reference genes Hprt and Rpl13a (Hamada et al., 2021). Data are shown normalized to Rpl13a, as the results did not differ when normalization was done with either reference gene.

**Estrous cycle measurements**

Estrous cycle stage was determined daily from 9 to 10 AM, prior to lights off, by obtaining vaginal smears as previously described (Satta et al., 2018). Vaginal smears were analyzed immediately by bright field microscopy using an EVOS® FL inverted microscope (Thermo Fisher Scientific).

![Figure 1](attachment:image.png)

**Figure 1** Mice in diestrus treated with a brain-penetrant selective estrogen receptor degrader (SERD) drink less EtOH in the drinking in the dark (DID) test. (A) Chemical structures for YL3-122 and XR5-27. (B) Mice (18 per group) underwent the DID test with 20% EtOH. Mice were treated with vehicle or the SERDs YL3-122 or XR5-27 on days 2 to 4 (indicated by arrows), 5 h prior to the drinking session. Graph shows g EtOH/kg body weight consumed during 2 h on days 1 to 4. *p < 0.05, comparing YL3-122 to vehicle and XR5-27 by post hoc Tukey’s test after two-way ANOVA. (C) EtOH consumption on days 2 to 4 separated by diestrus or estrus. **p < 0.01, comparing YL3-122 to vehicle in diestrus, #p < 0.05, comparing YL3-122 and XR5-27 in diestrus. Data are shown as the mean ± SEM.
RESULTS

Mice in diestrus treated with a brain-penetrant SERD drink less EtOH in the DID test

We previously demonstrated that ovariectomized mice treated systematically with 17β-estradiol consume more EtOH than vehicle-treated controls in the DID test (Satta et al., 2018) and that gonadally intact female mice with reduced estrogen receptor expression in the VTA consume less EtOH than control females in this test (Vandegrift et al., 2020). These results suggest that treating female mice with a SERD might be effective in reducing binge-like EtOH drinking. Female mice were treated with 50mg/kg of the brain-penetrant SERD YL3-122, an analogous low brain bioavailable SERD XR5-27 (Figure 1A), or vehicle daily beginning on the second day of drinking. We observed a significant treatment by day interaction in the 2-h drinking sessions on days 1 to 4 (Figure 1B; interaction: F [6, 203] = 2.45, p = 0.026), with YL3-122 treatment resulting in significantly reduced EtOH intake on day 4 (Tukey’s post hoc test, YL3-122 vs. vehicle, p = 0.034 and YL3-122 vs. XR5-27, p = 0.0006; Cohen’s d = 0.8). Treatment with XR5-27 did not affect EtOH intake when compared to vehicle treatment. We next examined the drinking data partitioned by whether mice were in diestrus or estrus on the three treatment days (days 2 to 4). Diestrus and estrus are hormonally distinct phases of the estrous cycle, with E2 levels higher during diestrus than estrus (Nilsson et al., 2015). Interestingly, mice treated during diestrus with YL3-122 drank less EtOH when compared to mice treated with vehicle and XR5-27 (Figure 1C; treatment, F (2, 61) = 4.98, p = 0.0099; treatment by phase interaction, F (2, 61) = 3.46, p = 0.038; post hoc Tukey’s test in diestrus mice: YL3-122 vs. vehicle, p = 0.0021 and YL3-122 vs. XR5-27, p = 0.04). YL3-122 had no effect on EtOH intake in mice in estrus (YL3-122 vs. vehicle and XR5-27, p = 0.97 and p = 0.68, respectively). After 4 h of drinking on day 4, the effect of YL3-122 on EtOH intake was no longer apparent (data not shown), which may be due to administration of the drug ~5 h prior to the drinking session (YL3-122 has a 4.5-h half-life). XR5-27 treatment had no effect on EtOH intake regardless of estrous cycle phase. These results indicate that a brain-penetrant SERD is effective in reducing binge-like EtOH drinking in mice in diestrus.

Female mice treated with a brain-penetrant SERD drink less sucrose in the drinking in the DID test

We next tested whether YL3-122 affects consumption of sucrose, another reinforcing substance. Female mice were treated with YL3-122, XR5-27, or vehicle and tested for 2% sucrose drinking using the same one-bottle procedure as for EtOH DID. Mice treated with YL3-122 consumed less sucrose than vehicle-treated mice (Figure 2A; treatment, F (2, 32) = 6.52, p = 0.004; day, F (3, 96) = 5.39, p = 0.0018; interaction, F (6, 96) = 3.87, p = 0.0017; Tukey’s post hoc test, YL3-122 vs. vehicle on days 3 and 4, p = 0.0002 and p < 0.0001, respectively). XR5-27 had no significant effect on sucrose intake when compared to vehicle. We next partitioned the data from treatment days 2 to 4 based on whether mice were in diestrus or estrus, although it should be noted that vaginal smears were only collected from a single cohort of six mice per group. We observed a trend toward a treatment effect but no treatment by phase interaction (Figure 2B; treatment, F (2, 20) = 3.20, p = 0.062; phase: F (1, 20) = 0.17, p = 0.68; interaction, F (2, 20) = 0.073, p = 0.93). Post hoc Tukey’s multiple comparisons test for main treatment effects indicated a trend toward decreased sucrose intake in mice treated with YL3-122 (p = 0.075) but not XR5-27 (p = 0.18). We next tested whether YL3-122 treatment would result in reduced water intake by performing a DID experiment with water only. YL3-122 did not reduce water drinking under these conditions (Figure 2C). YL3-122 also did not alter body weight over the course of the 4-day experiment (data not shown). Together, these results indicate that female mice treated with a brain-penetrant SERD consume less EtOH and sucrose under conditions that promote binge-like drinking.

SERDs do not affect blood EtOH clearance

To determine whether YL3-122 or XR5-27 alter EtOH metabolism or clearance, female mice were treated with the SERDs or vehicle 5 h prior to i.p. injection of 2 g/kg EtOH and blood was collected from the tail vein at various time points every 30 min up to 3 h after EtOH injection. YL3-122 and XR5-27 did not significantly alter BECs over the 3-h period (Figure 3), suggesting that the ability of YL3-122 to reduce EtOH intake was not due to an effect on blood EtOH clearance.

Esr1 gene expression is altered in a sex- and brain region-dependent manner after DID

Given that estrogen receptors are involved in EtOH drinking and the rewarding properties of EtOH (Hilderbrand & Lasek, 2018), we hypothesized that the expression of estrogen receptors could be altered by binge levels of EtOH exposure. Therefore, we examined transcript levels of Esr1 (the gene encoding ERα; note that Esr2 transcript, which encodes ERβ, was below the limit of detection) by qPCR in three different brain regions, the VTA, vHPC, and PFC in both female and male mice immediately and 24 h after 4 days of DID with EtOH or water as a control. In the VTA, Esr1 transcript was elevated immediately after the final drinking session irrespective of sex (Figure 4A; treatment, F (1, 19) = 4.74, p = 0.042; sex, F (1, 19) = 0.18, p = 0.68; interaction, F (1, 19) = 0.33, p = 0.57). In
the vHPC, Esr1 transcript was increased in males, but not females, immediately after the drinking session (Figure 4B; treatment, $F(1, 32) = 5.60, p = 0.024$; sex, $F(1, 32) = 2.67, p = 0.11$; interaction, $F(1, 32) = 7.48, p = 0.01$; post hoc Bonferroni’s test, water vs. EtOH in males, $p = 0.002$ and water vs. EtOH in females, $p = 0.4$). Esr1 transcript returned to control levels 24 h after EtOH drinking in all three brain regions (data not shown). These data indicate that Esr1 transcript levels are dynamically and differentially regulated in males and females after binge levels of EtOH intake in different brain regions.

**DISCUSSION**

We demonstrate here that treating female mice with a brain bioavailable SERD reduces binge-like EtOH intake, an effect that depends on estrous cycle phase. Specifically, treating mice during diestrus, when E2 levels are rising, reduces binge-like EtOH drinking,
whereas treating mice during estrus, when E2 levels have dropped, has no effect on ETOH consumption. These results are consistent with electrophysiological evidence from prior studies. Treating brain slices acutely with the SERD fulvestrant or the selective ER α antagonist MPP blocks the enhancement of VTA neuron firing rate by ETOH during diestrus and not during estrus (Vandegrift et al., 2017; Vandegrift et al., 2020), which could be relevant to binge ETOH drinking.

Although we did not treat male mice with SERDs in this study, we previously demonstrated that reducing levels of Esr1 or Esr2 transcript in the VTA of male mice has no effect on ETOH consumption (Vandegrift et al., 2020). However, SERD treatment could conceivably have an effect in males via inhibition of estrogen receptors in other brain regions than the VTA. Male and female mice express aromatase, the enzyme that converts testosterone to E2, throughout the brain, and synthesize E2 centrally from circulating testosterone (Yang & Shah, 2014). If ETOH consumption is modulated by E2 or estrogen receptors expressed in male brain, it is possible that SERD treatment could also reduce ETOH consumption in males. Interestingly, Blednov et al. tested the effect of systemic treatment with the SERM tamoxifen on two-bottle choice ETOH consumption in male and female mice and found that tamoxifen treatment decreased ETOH consumption in males in a peroxisome proliferator-activated receptor gamma (PPARγ)-dependent manner but had no effect in females. They attribute the effect of tamoxifen on ETOH consumption in males to the inhibition of repressive estrogen receptor binding at peroxisome proliferator-activated receptor (PPAR) DNA response elements, allowing for subsequent transcriptional activation by PPARγ (Blednov et al., 2016). Thus, multiple mechanisms involving estrogen receptors could alter ETOH drinking in males. More studies are needed to understand potential role of E2 and/or estrogen receptors in the male brain in ETOH intake.

The brain bioavailable SERD that we tested here (YL3-122) most likely acted in the central nervous system to reduce binge-like ETOH drinking in female mice because XR5-27, which has lower brain penetration, did not decrease ETOH drinking. These data suggest that brain and not peripheral estrogen receptors promote binge-like ETOH intake and are supported by results, showing that knocking down estrogen receptors in the VTA of female mice reduces binge-like ETOH drinking (Vandegrift et al., 2020). Neither of the SERDs impacted the rate of blood ETOH clearance, indicating that systemically inhibiting estrogen receptors does not alter ETOH metabolism.

In addition to reducing ETOH intake, YL3-122 (but not XR5-27) also significantly reduced sucrose consumption in a DID test. These results are interesting because they suggest that SERD treatment does not specifically impact binge ETOH drinking but may have general effects on either motivated behaviors and/or induce anhedonia. In terms of reward-related/motivated behaviors, estrogen is involved in binge eating, defined by the overconsumption of palatable food (food that is high in sugar, fat, or both) (Ma et al., 2020). Systemic E2 administration to ovariectomized rats and mice reduces consumption of palatable foods in binge eating tests (Cao et al., 2014; Micioni Di Bonaventura et al., 2017) and direct injection of E2 into the VTA of female rats reduces motivation for sucrose pellets (Richard et al., 2017), indicating that centrally acting E2 suppresses binge eating. It is possible that SERD treatment reduced sucrose consumption in the DID test by affecting “binge-eating”-like behavior although this seems contradictory to the known ability of E2 to suppress binge eating.

The other possibility is that YL3-122 treatment induced anhedonia or depression-like behavior in our mice. Rapid decreases in circulating E2, such as after ovary removal and during the postpartum period, are associated with depression in humans and treatment with combined E2 and antidepressants can alleviate depression symptoms more effectively than just antidepressant treatment (Borrow & Cameron, 2014; Dwyer et al., 2020). There is also some evidence that E2 administration (i.e., hormone replacement therapy) can improve depression symptoms in perimenopausal and early postmenopausal women (Borrow & Cameron, 2014; Dwyer et al., 2020). Studies in animals have

**FIGURE 4** Esr1 gene expression is altered in a sex- and brain region-dependent manner after drinking in the dark (DID). Mice underwent the 4-day DID procedure with 20% ETOH or water as a control. Mice were euthanized immediately after the last drinking session and the (A) ventral tegmental area (VTA, 6 female water, 7 male water, 4 female EtOH, 6 male EtOH), (B) ventral hippocampus (vHPC, 9 per sex per group) and (C) prefrontal cortex (PFC, 9 per sex per group) were dissected and RNA isolated for measurement of expression by Esr1 (a) ventral tegmental area (VTA, 6 female water, 7 male water, 4 female EtOH, 6 male EtOH), (B) ventral hippocampus (vHPC, 9 per sex per group) and (C) prefrontal cortex (PFC, 9 per sex per group) were dissected and RNA isolated for measurement of expression by Esr1 (a) ventral tegmental area (VTA, 6 female water, 7 male water, 4 female EtOH, 6 male EtOH), (B) ventral hippocampus (vHPC, 9 per sex per group) and (C) prefrontal cortex (PFC, 9 per sex per group) were dissected and RNA isolated for measurement of expression by Esr1 (a) ventral tegmental area (VTA, 6 female water, 7 male water, 4 female EtOH, 6 male EtOH), (B) ventral hippocampus (vHPC, 9 per sex per group) and (C) prefrontal cortex (PFC, 9 per sex per group) were dissected and RNA isolated for measurement of expression by Esr1
corroborated clinical findings, indicating a role for E2 in alleviating depressive-like behaviors (Borrow & Cameron, 2014). Notably, one side effect of fulvestrant is depression, supporting the notion that YL3-122 treatment induced anhedonia in our mice. The decrease in sucrose intake by YL3-122 treatment did not appear to be dependent on estrous cycle phase, in contrast to the ability of YL3-122 to reduce EtOH drinking specifically during diestrus. Further behavioral experiments are needed to disentangle a potential role for YL3-122 in behaviors related to binge eating and anhedonia.

In an effort to begin to understand molecular mechanisms that drive sex differences in binge alcohol drinking, we measured Esr1 transcript levels in the VTA, vHPC, and PFC after 4 days of DID. We found that Esr1 expression increased after binge levels of EtOH drinking, but that EtOH effects on Esr1 expression differed by sex in the PFC and vHPC. These results suggest sexually dimorphic effects of EtOH on gene transcription in the PFC and vHPC and might indicate sex differences in the role of Esr1 in behavioral responses to EtOH in these brain regions. It will also be important to determine whether chronic EtOH exposure alters estrogen receptor levels in the brain. Chronic alcohol use is associated with higher circulating E2 levels, which could in turn change the expression of estrogen receptors in the brain because of positive and negative feedback loops (Rachdaoui & Sarkar, 2017).

One neuroanatomical site for estrogen receptors in promoting binge drinking is the VTA (Vandegrift et al., 2020), although estrogen receptors could also act in other brain regions, such as the dorsal raphe, hippocampus, amygdala, or prefrontal cortex to alter binge eating and drinking behaviors (Cao et al., 2014; Ma et al., 2020). It will be important in future to determine where in the brain YL3-122 acts to reduce both binge-like EtOH and sucrose consumption, which could be done by microinjections into specific brain regions. Another limitation of this study is that we did not test the SERDs for their effect on EtOH consumption after mice had been drinking alcohol for a long period of time. It will be important to determine whether inhibiting estrogen receptors is effective in reducing alcohol drinking after a chronic drinking history, as this is more clinically relevant.

This study demonstrates that treatment with a brain bioavailable SERD can reduce binge-like drinking in female mice during diestrus. These results imply that SERD treatment could be an option for reducing binge drinking in women, but that hormonal status (menstrual cycle phase) may need to be taken into consideration in terms of timing SERD administration. It is interesting to note that higher levels of binge drinking (especially on the weekends) are associated with elevated E2 in the context of lower progesterone levels, such as during the ovulatory phase of the menstrual cycle. This suggests that SERD treatment might be more effective in reducing excessive drinking during ovulation than at other times (Martel et al., 2017). In addition, SERDs can disrupt the menstrual cycle, which can be an important consideration for some women. Finally, more preclinical studies are needed to determine whether YL3-122 is significantly associated with anhedonia or other depression-related behaviors, as this side effect would be unfavorable and preclude use in the clinic.

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CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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