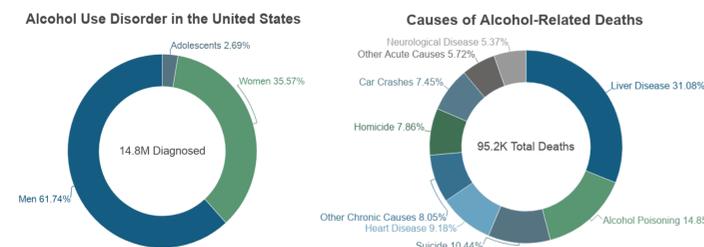# Development of a DSM-V Porcine Model of Alcohol Use Disorder

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Introduction

Alcohol Use Disorder in the United States — 14.8M Diagnosed

Causes of Alcohol-Related Deaths — 95.2K Total Deaths

AUD severity is significantly higher for equivalent exposure in females and generally develops over a shorter time than for men.

Less than 10% of people with past-year alcohol use disorder receive any treatment.
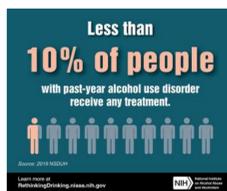
➢ AUD is a complex disorder and consequently, existing therapeutics are variable in their efficacy.
➢ Research into AUD has predominantly used rodent models.
➢ Before clinical trials can be performed in humans, the Food and Drug Administration requires that safety and efficacy is evaluated in another mammalian animal (the animal rule).

Pigs are a logical and tractable mammalian species for such investigations given their biological and physiological similarities to humans.

Preliminary Data
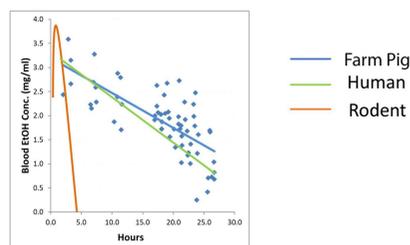
Figure 1. Swine metabolize ethanol similarly to humans while mice metabolism is about 10 times faster than humans or swine. The blue line was generated from our farm pig data, the green line is stylized human ethanol metabolism, and the orange line is stylized mouse ethanol from literatures.
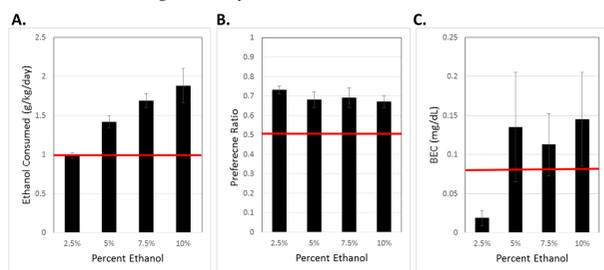
Figure 2. The farm pigs reached intoxication, free-choice binge drinking levels and showed a strong preference for ethanol solution over water.

Animal & Design

Figure 3. (A) Miniature swine for model development. (B) Two-Bucket Choice setup.

- Within-subject design with five mini-pigs in total.
- The Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) is the standard used to diagnose AUD in the clinic for humans.

Methods & Results

DSM-V Diagnosis:

Mild AUD: 2 to 3 Symptoms; Moderate AUD: 4 to 5 symptoms; Severe AUD: ≥6 symptoms.

| DSM-V	Pig 1	Pig 2	Pig 3	Pig 4	Pig 5
1	✓	✓	✓	✓	✓
2	✓	✓	✓	✓	✓
3	TBD	TBD	TBD	TBD	TBD
4	✓	✗	✗	✗	✗
5	✓	✓	✓	✓	✓
6	TBD	TBD	TBD	TBD	TBD
7	✗	✓	✗	✗	✗
8	TBD	TBD	TBD	TBD	TBD
9	✗	✗	✗	✗	✗
10	TBD	TBD	TBD	TBD	TBD
11	✓	✓	✓	✓	✓
Diagnosis	Moderate*	Moderate*	Moderate*	Moderate*	Moderate*

Table 1. The 11 DSM-V criteria for diagnosis of AUD. We tested 7 criteria, and out of those 7 criteria, all pigs presented with moderate AUD. If any of the pigs meet 1 out of the remaining 4 criteria, they will be classified as severe AUD. Together, our results highlight this novel pig AUD model is exciting avenue for the investigation of therapeutic strategies. [✓ = meets criteria, ✗ = does not meet criteria, TBD = to be done. *Moderate AUD using tasks to measure DSM-V criteria.]

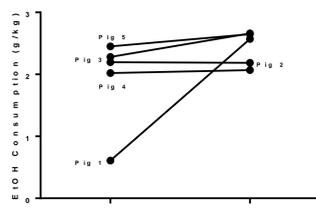### 1. Drinks larger amounts of alcohol than intended.
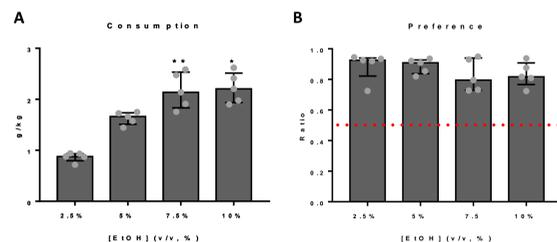
Figure 4. In a two-bucket free-choice test (A) alcohol consumption increased significantly as the ethanol concentration escalated; (B) a strong preference for alcohol compared to water was observed (ration greater than 0.5). [All pigs met criteria.]

2. Difficulty controlling drinking.
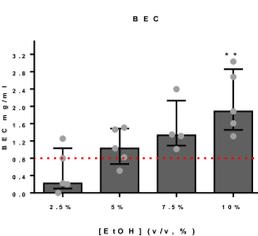
Figure 5. Blood ethanol concentrations (BEC) indicated that all pigs drank to intoxication under free-choice conditions, except at 2.5% EtOH. The red dashed line indicates the standard for alcohol intoxication (0.8 mg/ml). [All pigs met criteria.]

3. Spends a considerable amount of time drinking or recovering from drinking.

Figure 6. 24-hour video recording for time spend on sleeping or inactive. We hypothesized that AUD pigs will spend more time sleeping as ethanol concentration escalated. [TBD]
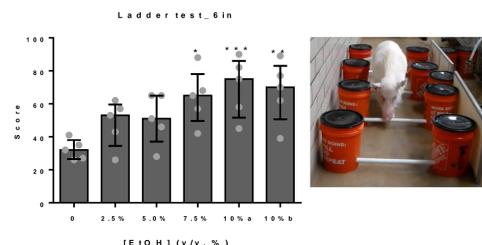
4. Craves alcohol.

Figure 7. After three days of restriction, the volume of alcohol consumed increased, in comparison to baseline drinking volumes, in pigs 1, 3, and 5 while pigs 2, and 4 remained stable. [Pig 1 met criteria.]

5. Fails to fulfill major roles/obligations due to alcohol use.


Figure 8. As ethanol concentration increased the agility score of the pigs decreased compared to baseline (0%). [All pigs met criteria.]

6. Continued alcohol use despite having persistence/recurrent social or interpersonal problems.

Figure 9. The greeting test. Pigs are social animals and interact readily with the investigators. We hypothesized that the level of interaction would decrease with increased ethanol consumption (volume and concentration). [TBD]

### 7. Recreational activity is given up or reduced because of alcohol use.
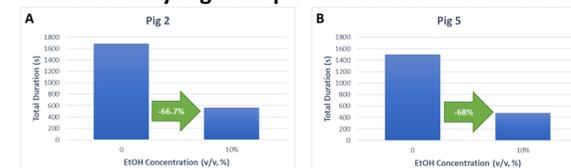
Figure 10. We observed a decrease in recreational activity within the home-pen as alcohol consumption increased, in two pigs. The remaining three pigs did not meet this criteria.

8. Recurrent alcohol use in physically hazardous situations.

Figure 11. The Shock collar test. We hypothesized that the pigs would continue drinking despite experiencing a mild electric shock, particularly as alcohol consumption increased. [TBD]

### 9. Continued alcohol use despite physical/psychological problems.
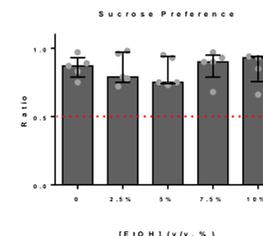
Figure 12. All pigs displayed a strong preference for sucrose in a two-bucket free-choice of either water or 0.5% sucrose. These results indicate that either these animals were not depressed or that this test is inappropriate for pigs. Further research is needed to adjudicate between these alternatives.

10. Development of pharmacokinetic/pharmacodynamics tolerance to alcohol.

Pharmacokinetic tolerance will be measured following a 1.5 g/kg dose of alcohol given by gavage of 15% ethanol in water. Blood samples will be taken in intervals throughout 24 hours and analyzed by Gas Chromatography. We hypothesized the mini-pigs will develop pharmacokinetic tolerance and that they will need to drink more alcohol to reach equivalent BEC levels. [TBD]

Pharmacodynamics tolerance will be evaluated by the agility test described in (5). We hypothesized that the performance of the task will improve once it developed. [No pig met criteria.]

11. Experiencing withdrawal symptoms when drinking is stopped.
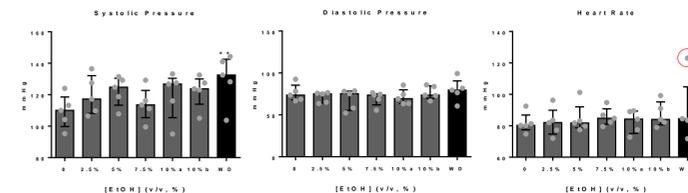
Figure 13. We evaluated multiple factors related to withdrawal symptoms including blood pressure, heart rate, body temperature, body weight, muscle twitch, time spending on sleep, Δ excrement. [We only observed a change in blood pressure and for Pig 2 tachycardia during abstinence (see red circle).]

Discussion

To date, all 5 pigs have been evaluated on 7 of the 11 DSM-V criteria for an AUD diagnosis in humans; a full severity assessment will be completed when the other 4 criteria are performed. Thus far, however, all 5 pigs satisfy the criteria for moderate AUD (4 to 5 symptoms of 11). These results highlight that mini-pigs can develop significant AUD when given free-choice alcohol exposure. Thus, the minipig may be an improved translationally relevant model species over rodents for pre-clinical evaluation of therapeutic strategies for AUD.

Acknowledgements