Effects of Aripiprazole Alone and in Combination with d-Amphetamine on Probability Discounting in Sprague-Dawley Rats

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Effects of Aripiprazole Alone and in Combination with \(d\)-Amphetamine on Probability Discounting in Sprague-Dawley Rats

Paige M. Currie

Thesis submitted
To the Eberly College of Arts and Sciences
at West Virginia University

in partial fulfillment of the requirements for the degree of

Master of Science in
Psychology

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Morgantown, West Virginia
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Keywords: probability discounting, risky choice, aripiprazole, \(d\)-amphetamine, polypharmacy

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Abstract

Effects of Aripiprazole Alone and in Combination with d-Amphetamine on Probability Discounting in Sprague-Dawley Rats

Paige M. Currie

Pharmaceuticals are helpful tools in aiding individuals with psychiatric diagnoses. Sometimes, the drug’s side effects can be more severe than the initial problem. Maladaptive behaviors, like pathological gambling, overeating, and substance abuse, are important to consider during the prescription of different pharmaceuticals, particularly those used to treat Attention-Deficit/Hyperactivity Disorder (ADHD) and autism spectrum disorder (ASD). Individuals with these diagnoses are often prescribed: stimulants, like d-amphetamine (d-AMP; for symptoms associated with ADHD), and antipsychotics, like aripiprazole (ARI; for symptoms associated with ASD). These drugs in combination could influence maladaptive behavior, including risky choice (probability discounting). The present study used eight, male Sprague-Dawley rats to examine effects of ARI, alone and in combination with d-AMP, on risky choice. Results demonstrate an interaction between the two drugs, indicated by an increase in risky choice over and above what either drug does alone. Drug combinations in behavioral research are understudied, hence it is imperative that we develop a better understanding of how drug combinations influence choice.
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Effects of Aripiprazole Alone and in Combination with d-Amphetamine on Probability Discounting in Sprague-Dawley Rats

Psychotropic drugs are helpful tools in aiding individuals with different mental health diagnoses. Oftentimes, however, the drug’s side effects can be more numerous and more severe than the initial problem. One side effect to consider is an increase in maladaptive behavior. Maladaptive behaviors, such as pathological gambling, overeating, and substance abuse, are important to consider during the development and use of different pharmaceuticals, especially in those that are being used to treat children who have Attention Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). Individuals with these diagnoses have been shown to engage in more risk-taking behaviors associated with more serious injuries than those without these diagnoses. Furthermore, this correlational research has been supported by differences in performance on risk-based laboratory decision-making tasks, such that individuals on the spectrum have engaged in more risky behavior (Cavalari & Romanczyk, 2012; Pollack et al., 2019).

According to the Centers for Disease Control and Prevention (CDC; 2019), approximately 1 in 59 children are diagnosed with ASD, and 1 in 20 children are diagnosed with ADHD. Furthermore, Antshel and Russo (2019) analyzed data from the CDC and found that approximately 1 in 8 children diagnosed with ADHD are also diagnosed with ASD. Individuals with these diagnoses can be prescribed two different types of medications that both act on the dopamine system: stimulants, such as d-amphetamine (d-AMP; Dexedrine®; to combat symptoms associated with ADHD), and antipsychotics, such as aripiprazole (ARI; Abilify®; to combat symptoms associated with ASD). Dopaminergic drugs such as these can impact responding for rewards and could in turn influence maladaptive behavior.
Dopamine is a neurotransmitter that is often associated with the brain’s “reward system,” and it has been implicated as a contributing factor in impulse-control disorders and risky behaviors (Schultz, 2013). A portion of the human research on risky choice has investigated behavior within the clinical population of individuals who have been diagnosed with Parkinson’s Disease, as this disease is characterized by death of dopaminergic neurons within the substantia nigra (Barzilai & Melamed, 2003). According to Djamshidian and colleagues (2011), individuals with Parkinson’s Disease who are taking a dopaminergic agonist often engage in behaviors associated with deficits in impulse-control, such as gambling, overeating, substance abuse, and compulsive shopping, compared to those who have not taken this type of drug. The occurrence of these behavioral patterns can be modeled through different choice-based behavioral measures in order to understand how drugs may impact decision making.

Discounting procedures are one of the measures used to assess risky choice. Several different discounting paradigms are used within the field of behavior analysis as a means of measuring optimal versus suboptimal choice, including probability discounting. During a probability-discounting procedure, choice is between a smaller, certain reinforcer (one food pellet at 100% probability; “safe” choice), and a larger, uncertain reinforcer (two or more food pellets at variable probabilities; “risky” choice), with the probability of the larger-reinforcer delivery decreasing across blocks of discrete trials. The percentage of larger-reinforcer choices across blocks are then plotted across the different probabilities, to create a probability-discounting curve. In humans, higher proportions of choice for the larger “risky” outcome (and shallower curves) are correlated with higher rates of maladaptive behavior, including compulsive gambling (Holt, Green, & Myerson, 2003).
Behavior related to risk has been shown to occur differentially across populations with and without intellectual and developmental disabilities. For example, hospitalizations due to injury, whether intentional or accidental, have been shown to be higher in individuals with intellectual and developmental disabilities compared to those without such disabilities (Calver et al., 2021), and can potentially be tied back to perception of injury risk (Bonander et al., 2016). Furthermore, children with ADHD have shown less probability discounting (more risky choice) compared to individuals who have not been diagnosed with ADHD (Drechsler et al., 2009; Marx et al., 2018; Wilson et al., 2010; Winstanley et al., 2006). In contrast, the research on probability discounting as a measure of risky choice demonstrated by individuals with ASD is limited (Paiva et al., 2019). Risk has been evaluated within individuals with ASD using different procedures, such as the Iowa Gambling Task (Bechara et al., 1994). In this task, participants are presented with four virtual decks of cards and are told that each deck will either reward them with more virtual money or penalize them by taking money away, and that they must try to win as much money as possible. Participants are not informed which decks produce favorable outcomes (“good” decks) versus unfavorable outcomes (“bad” decks), but rather they must contact the contingencies associated with each deck through repeated exposure to all of the outcomes. Research using this task has shown that compared to individuals without a diagnosis, individuals with ASD are slower to learn which deck produced optimal consequences and chose the losing deck more often, though it is unclear if these differences are due to reduced sensitivity to the contingencies or rigidity in patterns of switching among decks (Mussey et al., 2015). Knowing how choice may shift for individuals with these diagnoses, it is imperative that research is dedicated to investigating how behavior of such individuals may shift under the effect(s) of various drugs (such as ARI and d-AMP).
Probability discounting has been assessed for varying doses of \(d\)-AMP in Lewis and Fischer 344 rats, finding that relatively low doses (0.1-0.3 mg/kg) of the drug increased \textit{risky} choice, while larger doses (1.0-1.8 mg/kg) were associated with more omitted responses (Ozga-Hess & Anderson, 2019). Conversely, \(d\)-AMP and other stimulant drugs, which increase dopamine, have been shown to decrease \textit{impulsive} choice in delay-discounting procedures with Lewis and Fischer 344 rats (Huskinson et al., 2012). While both probability and delay discounting can measure some sort of suboptimal, and potentially maladaptive, choice, the different drug effects in the two procedures suggests that there may not only be differences in the procedures themselves, but also different neurobehavioral mechanisms that underlie these types of choice.

The \(D_2\) receptor within the dopamine system has been shown to be implicated in behaviors associated with drug abuse, as well as other behaviors associated with heightened impulsivity and risk-taking. According to Dalley et al. (2011), highly impulsive rats not only had fewer \(D_2\) and \(D_3\) receptors in the nucleus accumbens (an integral structure in the dopamine reward system), but also engaged in higher rates of cocaine self-administration, suggesting a possible relation between impulsivity, dopamine receptor availability, and self-administration of stimulant drugs. Additionally, Gabriel et al. (2021) demonstrated that the blockade of \(D_2\) receptors increases choice for probabilistic rewards as opposed to effortful ones. Whether these behavioral effects are due to existing structural features of the dopamine receptor, whether the changes to the receptors occur as a result of repeated and prolonged exposure to cocaine, or if something else entirely accounts for these effects is unknown; however, the neurological and neurochemical changes that yield behavioral effects associated with impulsivity are needed areas of study.
The atypical antipsychotic medication ARI operates on many neurotransmitter systems, but notably functions as a partial dopamine (D2) agonist. Partial agonists can act as both an agonist or an antagonist depending on the concentration of the corresponding neurotransmitter at baseline. For example, when levels of endogenous dopamine are low, ARI stimulates dopamine receptors like an agonist; and when levels of endogenous dopamine are high, ARI can block dopamine receptors, resulting in a net decrease in dopamine (Stępnicki et al., 2018). Dopamine and serotonin dysregulation have been shown to occur in patients diagnosed with schizophrenia, specifically contributing to positive symptoms (e.g., hallucinations; Brisch et al., 2014). When a drug changes the occurrence of undesired behaviors that are associated with dysfunction of a neurotransmitter, the activity of that particular drug may become a little clearer.

Many atypical antipsychotics are partial agonists, however individual drugs alter monoamine levels differently. For example, risperidone (Risperdal; a commonly prescribed drug for individuals with ASD) is thought to bind to serotonin receptors to a greater extent than other monoamines, whereas ARI is thought to bind to dopamine (and more specifically D2) receptors in addition to serotonin and other monoamines (Sumiyoshi, 2008). The increased propensity for ARI to bind to postsynaptic dopamine receptors combined with its partial agonistic properties suggest that there may be the potential for changes in probability discounting as a result from these changes in dopamine.

Although no known studies to date have investigated effects of ARI or risperidone on delay or probability discounting, findings from studies using different dopamine agonists may help to develop a hypothesis for how ARI may impact choice, as these drugs act on dopamine receptors in some capacity. For example, rats that were given pramipexole (a different dopaminergic agonist) chose the larger, yet probabilistic reinforcers more often than smaller,
certain reinforcers (i.e., engaged in more risky choice; Rokosik & Napier, 2012). Furthermore, more recent literature has found that impulsive and compulsive spectrum disorders (e.g., gambling disorders, addiction) were increased following agonistic action at D$_2$ and D$_3$ receptors (Napier et al., 2020). It is important to note, however, that the drugs tested in these, and other, studies have largely been full agonists acting on the D$_2$ family of receptors, as opposed to partial agonists, such as ARI.

The primary FDA-approved use for ARI is for the treatment of schizophrenia; however, it is also approved for a number of other clinical populations, including individuals with depression, bipolar disorder, and Tourette’s Disorder (Otsuka Pharmaceuticals, 2020). In more recent years, it has been used to reduce aggression and irritability in individuals diagnosed with ASD (FDA, 2018; Otsuka Pharmaceuticals, 2020). Because of the common practice of pharmacologically treating patients with this diagnosis (in combination with behavioral interventions), individuals who have multiple diagnoses are often prescribed a “cocktail” of medications to take, sometimes pushing upwards of six different medications (Vohra et al., 2016). The only psychotropic drugs that have been approved by the FDA for the treatment of ASD are risperidone and ARI (FDA, 2018). Because ARI alters the dopamine system to a greater extent than risperidone (Sumiyoshi, 2008), it may potentially alter probability discounting differentially. In knowing that individuals with ASD (alone or with an additional diagnosis of ADHD) may engage in more risky choice, understanding how drugs commonly prescribed for ASD impact choice is imperative for the development of behavioral and medical interventions.

Several studies have been published showing that there may be a relation between increased risky behaviors, such as pathological gambling and risky sexual behaviors, and administration of ARI (Cohen et al., 2011; Gaboriau et al., 2014; Mété et al., 2016). The only
study published to date to model polypharmacy for individuals with ASD by studying effects of drug interaction between ARI and a psychostimulant on behavior in rats was published by Schwabe and Koch (2007). In this study, rats were tested on a progressive-ratio (PR) schedule, in which the response ratio that must be completed to obtain a reinforcer increases after the preceding ratio has been completed (the number of responses required to obtain a reinforcer increases after each reinforcer delivery, starting with one, then two, then four, then eight, etc.), and the point during a session at which responding stops for a pre-set period of time is deemed the breakpoint. After obtaining a stable baseline breakpoint, rats were divided into two groups and were administered ten injections of increasing doses of *d*-AMP or ten injections of saline. These injections took place three times a day in the home cage, over the course of four days with only one injection being administered on the final day. Twenty-four hours after the tenth injection, the two groups were each divided into two, resulting in a total of four groups. Two of the groups were exposed to ARI or saline, to observe the effects of ARI on *d*-AMP withdrawal, using the PR schedule again. Results showed that breakpoint was lower during *d*-AMP withdrawal compared to baseline. This difference was mitigated by low dose ARI (0.25-0.75 mg/kg). Higher doses of ARI, however, reduced breakpoint below its baseline levels (Schwabe & Koch, 2007). In summary, *d*-AMP increased the number of consecutive responses that rats would complete to obtain a reinforcer relative to baseline, suggesting that *d*-AMP may alter the absolute reinforcing value of the food pellets. ARI reduced consecutive responses to previous baseline levels or lower, suggesting that ARI may alter the reinforcing value or the motivating operation to respond.

**Statement of the Problem**
Because of the comorbidity of ASD and ADHD, the increased propensity for risk associated with these diagnoses, and the potential maladaptive effects that medication combinations may have on choice, investigating effects that pharmaceutical drug interactions may have on probability discounting is crucial. Preliminary research findings have shown that low dose d-AMP can increase risky choice (Ozga-Hess & Anderson, 2019). Although no studies have experimentally studied effects of ARI independently, or in combination with d-AMP on probability discounting, there are numerous case studies suggesting that there may be an association between ARI prescription use and increased compulsive behaviors, such as problematic gambling, risky sexual decisions, and problematic shopping (Cohen et al., 2011; Gaboriau et al., 2014; Mété et al., 2016). Because both drugs act on dopaminergic receptors, there is reason to believe that these drugs will influence choice. If we can develop a greater understanding of how these two medications affect choice in a probability-discounting paradigm, the results may improve our understanding of the behavioral effects of these drugs in a clinical setting.

**Experiment 1**

The purpose of Experiment 1 was to assess effects of ARI administration alone on risky choice in a probability-discounting procedure.

**Method**

All procedures were approved by the Animal Care and Use Committee at West Virginia University. Procedures have been carried out in compliance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC).

**Subjects**
Eight drug naïve, adult male Sprague-Dawley rats were pair-housed in controlled environmental conditions (temperature, 24°C; 12-h reverse light/dark cycle) with access to water *ad libitum*. Sessions were conducted around the same time each day, five days per week (Monday-Friday). Approximately 30 min after the session ended, rats were given about two hours of food access, resulting in roughly 22 hours of food restriction before the start of the next experimental sessions. On weekends, rats were fed the amount typically consumed in post-session.

**Apparatus**

Sessions were conducted in eight standard operant-conditioning chambers for rats, each enclosed in a melamine sound-Attenuating cubicle (Med Associates, VT). Each chamber contained a working area of 30.5 cm by 24.5 cm by 21.0 cm, a grid floor, and a 45-mg pellet dispenser with a pellet receptacle centered between two retractable response levers. Levers were 11.5 cm apart from each other and required at least 0.25 N of force for a response to be recorded. Levers were 4.8 cm wide, extended 1.9 cm into the chamber, and were elevated 8 cm from the grid floor. Two 28-V stimulus lights, 2.5 cm in diameter, were located approximately 7 cm above each lever. Each chamber had a 28-V houselight on the wall opposite to the working wall, and a ventilation fan to circulate air and to mask extraneous noise. Data collection and programmed consequences were controlled by a personal computer equipped with Med-PC® software (Med Associates, VT).

**Procedure**

All sessions began with a 10-min blackout period, in which the ventilation fan was on, no levers were extended, and no lights were illuminated.
Preliminary Training. All rats acquired lever pressing as a part of an acquisition study prior to the beginning of this experiment. Before the probability-discounting procedure, training sessions were completed to expose choice to the probabilities used. During these sessions, 90 trials were initiated once every 40 s, with each trial consisting of a randomly determined lever extending into the chamber. If a response occurred within 10 s of the trial onset, a pellet was delivered at 50% probability, the lever retracted, the cue light and houselight turned off simultaneously, and a variable intertrial interval (ITI) initiated (e.g., if a lever press occurred within 8 s, the ITI was 32 s). If a response did not occur within 10 s of the onset of a trial, the lever retracted, the houselight and cue light turned off, and an omission was recorded. Trials continued until 45 responses occurred for each lever. Training continued for a minimum of five sessions, or until there were fewer than 10 omitted trials for two consecutive sessions. After meeting the criterion, the full probability-discounting procedure was used for the remainder of the experiment.

Probability-discounting procedure. Following the blackout period at the start of the session, five blocks of 24 trials each (16 forced-exposure and 8 free-choice) were presented. Each block began with 16 forced-exposure trials (eight on each lever). During each forced-exposure trial, the houselight turned on (after the ITI), one lever (randomly determined) extended into the chamber and the cue light above it turned on. After a response on the lever occurred, either one pellet was delivered at 100% probability or two pellets was delivered with one of the following probabilities: 100%, 50%, 25%, 12.5%, and 6.3% across blocks, with a different probability of larger-reinforcer delivery within each block. Choice was exposed to four out of the five probabilities of reinforcement during forced-exposure trials in each session; for the last block of trials, choice was exposed to the 6.25% probability of delivery every other session, on
average. The houselight flashed for 0.1 s as each food pellet for the larger alternative was delivered. Levers that are paired with each reinforcer size (one vs. two pellets) were consistent throughout the experiment for each individual rat, but counterbalanced between groups (e.g., Rats 1-4 had larger, uncertain food pellets paired with responses on the left lever, while Rats 5-8 had the larger, uncertain food pellet delivery paired with responses on the right lever). Following a response, the lever retracted and the cue light turned off simultaneously, the houselight turned off, and pellet(s) would be delivered according to the contingency in place for that block of trials.

Lever presentation during forced-exposure trials was semi-randomly sampled with replacement, with the constraints that each lever must be presented eight times within a block and that the same lever should not be presented on more than two consecutive trials. The probability of larger-reinforcer delivery during forced-exposure trials was determined by the trials in a block, meaning that if the probability of larger-reinforcer delivery was 50%, the larger reinforcer would be delivered during four out of the eight forced-exposure trials for the larger, uncertain lever.

Each set of forced-exposure trials in a block were followed by eight free-choice trials, during which both levers were extended into the chamber, cue lights illuminated over each lever, the houselight turned on, and choice was recorded. The probability of larger-reinforcer delivery was independent during free-choice trials, such that the probability of delivery on any given trial was the same regardless of the outcome of the preceding trial. After a lever press occurred, cue lights turned off and levers were withdrawn simultaneously, and one or two food pellets were delivered (according to the aforementioned corresponding probabilities), depending upon which lever was pressed. After the food pellet(s) was delivered, a 20-s ITI began.
If a response did not occur within 10 s of the initiation of a trial for either category (i.e., forced or free), it was considered an omission. When an omission occurred, the houselight and cue light(s) were turned off, the lever(s) were retracted, and a 20-s ITI began. Sessions were considered complete after 120 total trials (80 forced-exposure and 40 free-choice), or 60 min, whichever occurred first. Any sessions with more than 20 omissions during free-choice trials were excluded from analyses.

**Stable Baseline Assessment.** Baseline probability discounting was determined by decreasing the probability of larger-reinforcer delivery across successive blocks of trials within sessions, independent of choice. During the first block of trials across sessions, a discrete-trial choice procedure was in effect (a fixed-ratio 1 schedule; one lever press required to obtain a reinforcer) for responses on both levers, with both reinforcer magnitudes (one or two food pellets) delivered with 100% probability. The probability of larger-reinforcer delivery decreased across blocks of trials according to the aforementioned sequence. A minimum of 20 sessions were conducted to obtain stable baseline probability discounting. To evaluate the stability of baseline responding, visual inspection and two-way analysis of variance (ANOVA) were conducted, in which the independent variable was probability of larger-reinforcer delivery by block, and the dependent variable was percent larger-reinforcer choice. In order for responding to be deemed stable, there must have been no increasing or decreasing trends in total percent choice for the larger-reinforcer during free-choice trials, an average of at least 80% choice (seven out of eight free-choice trials) for the larger reinforcer during the 100%-probability block in each session, the presence of a main effect of trial block, the absence of a main effect of session, and the absence of an interaction between session and trial block.
**Drug administration.** Once baseline responding on the probability-discounting procedure was stable, drug(s) and vehicle control (dimethyl sulfoxide [DMSO] in 3 mL strawberry Jell-O™ tablets by mouth) were administered. Due to the insolubility of ARI in distilled water and the inability to inject pure DMSO, ARI was weighed out based on the current weights of the rats (mg/kg) and the dose(s) being administered, and then dissolved in DMSO. The ARI solution was then measured to 1 mg/ml volume and portioned into individual wells of strawberry Jell-O™ solution. Control sessions took place on Mondays and Thursdays, and drug or vehicle administrations took place on Tuesdays and Fridays, with the stipulation that choice during the 100%-probability block was at least 80%, and total percentage of larger-reinforcer choice was within the range of the last five baseline sessions during the most recent control session. The DMSO vehicle was given at least twice prior to Experiment 1 drug administration to evaluate behavioral interference due to administration procedures alone and continued until no disruptions occurred.

On each administration day, rats received one of a series of doses of ARI (0.0 – 10.0 mg/kg delivered by mouth (p.o.)) 30 min prior to the start of the session, creating a 40-min pretreatment period. Each dose was administered at least twice, and additional administrations took place when there was substantial variability in choice following the two primary administrations. Sessions were conducted to obtain data to complete the dose-response function twice.

**Drugs**

ARI was purchased from Sigma-Aldrich (St. Louis, MO). ARI was dissolved in DMSO and combined with 3 mL of strawberry Jell-O™ solution in order to be administered p.o.

**Data Analysis**
Dependent Measures.

**Percent Larger-Reinforcer Choice.** The primary dependent variable was percent larger-reinforcer choice. This measure was calculated by dividing the number of free-choice responses on the lever associated with the larger, uncertain reinforcer by the total amount of free-choice responses made per session block. Percent larger-reinforcer choice was plotted as a function of decreasing probability of larger-reinforcer delivery to obtain probability-discounting curves.

An additional analysis of percent larger-reinforcer choice was conducted by assessing responses made in the last three blocks of a session, where the probability of larger-reinforcer delivery was at its lowest and responses on the larger lever were less likely to result in a reinforcer delivery (i.e., more risk for larger reinforcer choice in last three blocks relative to first two blocks). This analysis was conducted by dividing the number of responses made for the larger-reinforcer in the last three blocks of a session by 24 (the total amount of free-choice responses that could be made during the last three blocks) and multiplying by 100 to obtain a percentage.

**Discounting Rate (h) and Indifference Points (IPs).** Estimates of h and IPs were interpolated from model fits of percent larger-reinforcer choice based on the hyperbolic formula developed by Mazur for delay discounting (1987), shown below.

$$V = \frac{A}{(1 + h\Theta)}.$$  

In this equation, $V$ is the subjective value of the larger, uncertain reinforcer at an amount of $A$ (reinforcer magnitude), and $h$ is a free parameter that represents rate of probability discounting (i.e., the slope of the discounting function). $\Theta$ is odds against receipt of the reinforcer, calculated as $(1-p)/p$, where $p$ is the probability of receiving the larger reinforcer. Subjective value of the
larger reinforcer is plotted as a function of the odds against its receipt. Larger $h$ values characterize steeper probability-discounting functions, and indicate a higher rate of discounting, or more risk-averse choice.

Within this experiment, average percent larger-reinforcer choice during the first block of trials was used as an estimate of the $A$ parameter. IPs were transformed to reflect indifference to probability of larger-reinforcer delivery (as opposed to odds against reinforcer delivery or the ratio of the number of trials that would not “pay off” compared to how many trials would), so lower IPs are associated with more risky choice. Smaller $h$ values correspond with more shallow functions and higher levels of risky choice.

**Area Under the Curve (AUC).** AUC was calculated for discounting rates using the formula described by Myerson et al. (2001). The AUC calculation involves drawing vertical lines from each data point of the discounting curve to the x-axis, dividing the graph into four trapezoids. AUC is obtained by adding the areas of each of the trapezoids. AUCs can range from 0.0 (exclusive choice for the smaller, certain reinforcer) to 1.0 (exclusive choice for the larger, uncertain reinforcer), with larger AUC values corresponding with more risky choice. AUC was calculated for the entire session, as well as for the last three blocks when choice for the larger reinforcer was less likely to be delivered, relative to the prior blocks.

**Win-Stay/Lose-Shift Ratios.** To evaluate reinforcer sensitivity and negative feedback, win-stay and lose-shift analyses were conducted, respectively. Individual trials within each session were evaluated according to the choice (i.e., smaller, certain or larger, uncertain) and outcome (i.e., reinforcer or no reinforcer delivered) of each preceding trial. For win-stay ratios, the number of choices for the larger, uncertain alternative following a “win” on the preceding trial were divided by the total number of free-choice trials that resulted in a “win” on the larger,
uncertain alternative. Larger win-stay ratios indicate greater sensitivity to reinforcer delivery. For lose-shift ratios, the number of choices for the smaller, certain alternative following a “loss” on the preceding trial were divided by the total number of free-choice trials that resulted in a “loss” on the larger, uncertain alternative. Larger lose-shift ratios indicate greater loss aversion.

**Statistical Analyses.** Two-way repeated-measures analysis of variance (ANOVA) were conducted to analyze effects of session block and ARI dose on percent larger-reinforcer choice. One-way repeated-measures ANOVAs were used to examine effects of ARI dose on percent larger-reinforcer choice last three blocks, percent larger-reinforcer choice for the whole session, \( n \) estimates, IPs, AUC, win-stay ratios, and lose-shift ratios. Greenhouse-Geisser (1959) corrections were used to adjust for violations of the sphericity assumption as needed. For significant main effects and interactions, Tukey’s Honestly Significant Difference (HSD) post hoc tests were used to make pairwise comparisons. For all statistical analyses, significance was defined as \( p < .05 \).

**Results**

**Baseline**

As the probability of larger-reinforcer delivery decreased, so did the number of responses emitted for the larger reinforcer, indicating that behavior was sensitive to the programmed contingencies (see Figure 1). A significant main effect of trial block indicated that discounting of reinforcers delivered on a probabilistic basis did occur, indicated by more responses for the larger-reinforcer high probabilities of delivery (i.e., 100.0 and 50% blocks) and fewer responses for the larger-reinforcer at relatively low probabilities (i.e., 25%, 12.5%, and 6.25% blocks). These data violated assumptions of sphericity and were transformed using a Greenhouse-Geisser correction \([F(1.5, 10.5) = 79.4, p < .001] \).
Percent Larger-Reinforcer Choice

Figure 2 shows mean percent larger-reinforcer choice as a function of probability of delivery across blocks at each dose of ARI. Similar to baseline responding, larger-reinforcer choice decreased as a function of probability of delivery regardless of ARI dose \[F(4, 28) = 62.49, p < .001\]. Although ARI did not impact discounting curves across all blocks, risky choice was reduced in the initial two blocks of trials and increased in the last three blocks, resulting in a flattening of the discounting function. This is change in choice is further evident by the presence of a significant ARI dose-by-block interaction \[F(12, 84) = 4.25, p < .001\]. Subsequent post-hoc comparisons revealed that 3.0 mg/kg of ARI \([M = 81.12, SD = 18.13]\) decreased percent larger-reinforcer choice in the first block relative to DMSO (vehicle) \([M = 97.66, SD = 18.13]\) and 10.0 mg/kg of ARI \([M = 22.16, SD = 18.13]\) increased percent larger-reinforcer choice relative to DMSO (vehicle) in block 4 \([M = 3.91, SD = 18.13]\). Despite the statistical significance of the dose-by-block interaction, reduced control of behavior by the consequences in the first block of trials (i.e., choice for the larger reinforcer dropping below 80% when there was a 100% probability of delivery) render these results difficult to interpret.

In order to assess effects of ARI when choice for the smaller, certain reinforcer across the eight trials would yield more overall reinforcers than responding exclusively for the larger, uncertain reinforcer, additional analyses were limited to the last three blocks of trials in which choice was more “risky” relative to choice in the first two blocks. Figure 3a shows mean percent larger-reinforcer choice across session as a function of each dose of ARI and Figure 3b shows mean percent larger-reinforcer choice across the last three blocks as a function of each dose of ARI. At the session-wide level, ARI did not significantly change the number of responses made for the larger reinforcer. When examining just the last three blocks, the highest dose of ARI
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(10.0 mg/kg) increased risky choice (i.e., an average of about 5.48 responses for the larger reinforcer) compared to vehicle (i.e., an average of 2.85 responses for the larger reinforcer) specifically in these last three blocks when the probability of larger-reinforcer delivery was at its lowest. There was a significant effect of dose \[ F(3,21) = 4.54, p = .013 \], such that 10.0 mg/kg of ARI \[ M = 5.48, SD = 2.79 \] increased choice for the larger-reinforcer relative to the DMSO (vehicle) \[ M = 2.85, SD = 2.79 \]. The increase in risky choice within the last three blocks combined with the reduced control in the first block warrants further study to clarify how ARI impacts choice or alters stimulus control.

**Area Under the Curve (AUC)**

Similar to analyses for percent larger-reinforcer choice, comparisons for AUC were made for the session as a whole and for the last three blocks of trials. Figures 4a and 4b show mean session-wide AUC as a function of each dose of ARI and mean AUC for the last three blocks, respectively. In general, AUC for the whole session was relatively stable across doses of ARI, which is consistent with the flattening of the discounting function. However, when analyses were limited to the last three blocks, 10.0 mg/kg increased AUC (and risky choice) compared to vehicle (a statistically significant difference that was not seen when looking at the session as a whole).

Statistical analyses showed that there was a significant effect of ARI dose for AUC as a session-wide measure \[ F(3,21) = 4.18, p = .018 \] and when AUC was calculated for choice in the last three blocks when larger-reinforcer choice was guaranteed \[ F(3,21) = 7.18, p = .002 \]. Pairwise comparisons indicated that ARI did not significantly change AUC compared to vehicle when analyses were run with AUC as a session-wide measure, but rather differed among doses.
When only looking at AUC for the last three blocks, 10.0 mg/kg ARI \[M = 0.234, SD = 0.106\] significantly increased AUC relative to the DMSO vehicle \[M = 0.074, SD = 0.106\].

**Indifference Points (IPs)**

There was an increase in IPs (reduced risky choice) at all three doses of ARI relative to the DMSO vehicle, but only 3.0 mg/kg ARI significantly changed IP. Figure 5 shows mean IPs as a function of each dose of ARI. There was a significant effect of dose during the acute condition \[F(3,18) = 4.96, p = 0.011\]. Pairwise comparisons indicated that 3.0 mg/kg ARI \[M = 61.70, SD = 20.68\] significantly increased IPs, relative to the DMSO vehicle \[M = 38.60, SD = 20.68\]. Larger IPs are associated with less risky choice and fall farther left on the curve. As indicated in this figure, 3.0 mg/kg ARI yielded a larger average IP compared to the DMSO vehicle, suggesting reduced risky choice.

**Discounting Rate (h)**

Figure 6 shows discounting rate \(h\), which corresponds to the slope of the discounting functions, ranging from 0.49 to 1.35. There was no significant effect of dose of ARI on discounting rate \[F(3, 21) = 1.03, p = 0.401\].

**Win-Stay and Lose-Shift Ratios**

In measures used to detect sensitivity to reinforcer delivery (win-stay), ARI significantly increased responding on the lever associated with the larger, uncertain reward following a win (Figure 7a: win-stay \[F(3,21) = 5.17, p = 0.008\]) relative to the DMSO vehicle. Additionally, in measures used to detect loss aversion (lose-shift), ARI significantly increased changing responses from the lever associated with the larger, uncertain reward to the smaller, certain reward following a loss (Figure 7b: lose-shift \[F(3,18) = 6.97, p = 0.003\]) relative to the DMSO vehicle. These results combined suggest that ARI may increase sensitivity to the contingencies of
probabilistic reinforcement, such that responding on the lever associated with an uncertain consequence tends to be greater following a win, and tends to decrease following a loss, relative to the DMSO vehicle.

Discussion

The purpose of Experiment 1 was to assess effects of ARI administration alone on risky choice in a probability-discounting procedure. Larger-reinforcer choice systematically declined as a function of decreasing probabilities of delivery during all conditions, indicating that choice was sensitive to the programmed contingencies of the procedure. When looking at when the average “payout” for the larger reinforcer was less than the average payout for the smaller reinforcer (i.e., Blocks 3, 4, and 5), ARI administration increased responses for the larger reinforcer, thereby increasing risky choice. Corresponding with this finding, an overall flattening of the function was noted, particularly at the highest dose of ARI, suggesting a potential reduced sensitivity to the magnitude of the reinforcers in the earlier blocks, or the contingencies corresponding to their delivery. These results were replicated and supported by analyses of AUC, with no significant differences noted for analysis of the whole session and significant increases when looking at the last three blocks, thereby demonstrating convergent validity.

Despite these findings, at the highest dose of ARI (10.0 mg/kg), choice within the first block dropped below 80% larger-reinforcer choice, indicating reduced control by magnitude of the reinforcer, and therefore rendered these data difficult to interpret. This value, however, is arbitrary, but was established by precedent in the literature. Responding equally across the available options (four for each option over repeated presentations) would be the means by which indifference is identified. Data that approach this split allocation of responses can be said to indicate reduced sensitivity to the magnitude of the reinforcer.
Another potential mechanism by which ARI may affect choice is through the disruption of stimulus control more broadly. Stimulus control can be defined as a behavioral phenomenon in which certain behavior occurs in the presence of certain stimulus conditions and differently in other stimulus conditions. For the purpose of this experiment, stimulus conditions consist of the differential cues for the two consequences (e.g., the flashing light for the larger-reinforcer delivery, changing probabilities, auditory feedback of two pellets dropping, reinforcer magnitude, etc.). Future research should be devoted to investigating how ARI administration may impact stimulus control in other capacities (e.g., reversal learning paradigms, observing responses, conditional discriminations).

Risk can be defined as “knowing” the probability of reinforcement for a given response, whereas ambiguity refers to contexts in which the probability of reinforcement is unknown. When considering stimulus control, it may be worthwhile to consider differences in these two constructs, and the extent to which they may be related to multiple (signaled) and mixed (unsignaled) schedules of reinforcement, respectively. The delineation between risk and ambiguity has only been investigated with humans with and without a diagnosis of ASD thus far. Risky choice has been defined as choice in which the probabilities are known while ambiguous choice is still probabilistic, but the probabilities of success are unknown (Fujino et al., 2017). Research should continue to investigate the importance of signaling or not signaling the probabilities of reinforcement across schedules with equal reinforcement rates. These different types of uncertainty have been associated with both overlapping (e.g., anterior insula) and distinct (e.g., dorsomedial prefrontal cortex and ventral striatum for risk and dorsolateral prefrontal cortex and inferior parietal lobe for ambiguity) neural structures, indicating that these processes are related, but not identical (Wu et al., 2021). As such, these differences in neural
activity may suggest that the presence or absence of stimuli signaling the probability of reinforcer delivery could differentially impact probability discounting. Additionally, the activation of the inferior parietal lobe has been shown to differ across individuals with ADHD and ASD relative to individuals who are typically developing (Sáenz et al., 2020). In considering the results of these studies together, it is possible that differences in the inferior parietal lobe activity may be associated with differences in how individuals with ADHD and ASD respond under “ambiguous” reinforcement contingencies. Further research should investigate the role of activation of these structures in choice-based tasks in both basic and applied research, and the extent to which different medications, such as ARI, may ameliorate or exacerbate these differences.

**Experiment 2**

Experiment 2 was conducted to determine the interaction of two different classes of drugs used for the treatment of comorbid ADHD and ASD. This experiment was designed to replicate and extend the findings of Experiment 1, by assessing effects of ARI administration, alone and in combination with d-AMP, on risky choice in a probability-discounting procedure.

**Method**

**Subjects**

The same eight adult male Sprague-Dawley rats from Experiment 1 were used in Experiment 2 and were kept in the same housing conditions.

**Apparatus**

The same eight operant-conditioning chambers from Experiment 1 were used in Experiment 2. Data collection and programmed consequences were controlled by the same personal computer equipped with Med-PC® software (Med Associates, VT).
**Procedure**

Procedures in Experiment 2 were identical to those of Experiment 1, with the exception of drug administration.

**Drug administration.** In Experiment 2, two doses of \(d\text{-AMP}\) (0.3 and 0.56 mg/kg) and SAL vehicle were administered in combination with three doses of ARI (3.0, 5.6, and 10.0 mg/kg) and DMSO vehicle. On each administration day, rats received ARI or vehicle in Jell-O™ solution, followed by one of the doses of \(d\text{-AMP}\) or vehicle 30 min later via i.p. injection, resulting in the same 40-min pretreatment window for ARI and a 10-min pretreatment window for \(d\text{-AMP}\) (see Figure 8 for a diagram outlining all drug combinations). Each drug-dose combination was administered at least twice (starting with DMSO/SAL, then \(d\text{-AMP}\) doses, then stepping through increasing doses of ARI in a similar manner; Figure 8), and additional administrations took place if there was substantial variability in choice between the two initial administrations.

**Drugs.** \(d\text{-AMP}\) was purchased from Sigma-Aldrich (St. Louis, MO). \(d\text{-AMP}\) was delivered in a 0.9% saline vehicle via i.p. injection.

**Data Analysis**

Data analytics in Experiment 2 were identical to those of Experiment 1, with an additional analysis of percent change from administration with vehicle.

**Percent-Change from \(d\text{-AMP}\) Administration.** Percent-change from \(d\text{-AMP}\) administration with vehicle was calculated in order to determine the extent to which ARI altered choice within the last three blocks beyond the effects of \(d\text{-AMP}\) alone. Analyses were completed as such to capture when choice within the blocks when reinforcer delivery was less likely to be delivered, as well as to minimize the likelihood that percent-change would be inflated by
increases from zero responses for the larger reinforcer (i.e., it was more likely that at least one response would occur across the three blocks when aggregated).

**Results**

**Percent Larger-Reinforcer Choice**

Consistent with baseline and Experiment 1 results, larger-reinforcer choice decreased as a function of probability of delivery (See Figures 9 and 10; \[F(4, 28) = 453.6, p < .001\]). When looking at how ARI influenced choice, we replicated the results from Experiment 1 without loss of control in the first block (i.e., there were no significant changes to percent larger-reinforcer choice following administration of each dose of ARI with SAL, indicated by similar probability-discounting functions in Panel A of Figure 10). \(d\)-AMP dose dependently increased percent larger-reinforcer choice, regardless of whether it was combined with a dose of ARI or the DMSO vehicle, supported by visual inspection of panels A, B, C, and D in Figure 9 (i.e., the data paths with dotted and dashed lines are higher on the graph relative to the data path with the solid line) and a significant main effect of \(d\)-AMP dose \([F(2,14) = 6.23, p = .012]\).

Choice for the larger reinforcer was augmented when \(d\)-AMP was combined with ARI compared to administration with the DMSO vehicle. For these visual inspections, compare the data paths with closed data symbols (administration with various ARI doses) to the data path with open symbols (administration with the DMSO vehicle) in Figure 10. Panel A shows data for combination with the SAL vehicle (all data paths for combination with SAL have solid lines), Panel B shows data for combination with 0.3 mg/kg \(d\)-AMP (all data paths for combination with 0.3 mg/kg \(d\)-AMP have dashed lines), and Panel C for 0.56 mg/kg \(d\)-AMP (all data paths for combination with 0.56 mg/kg \(d\)-AMP have dotted lines). These augmentative changes in percent larger-reinforcer choice are indicated by dashed or dotted data falling higher up on the graph.
relative to the data paths with solid lines, and these comparisons were found to be statistically significant [ARI*d-AMP Interaction: $F(6,42) = 2.42, p = .043$; ARI*d-AMP*Block Interaction: $F(24,168) = 2.09, p = .004$]. Conclusions of augmentative effects were supported by patterns seen in the data using visual analysis, and this pattern was noted for comparisons across dependent variables.

When examining larger-reinforcer choice as a global measure, the highest dose of $d$-AMP (0.56 mg/kg) increased risky choice relative to the DMSO vehicle, indicated by increases across the shading of bars in Figure 11a. These changes in behavior are further supported by a significant main effect of $d$-AMP dose, corrected with a Greenhouse-Geisser transformation [$F(1.17, 8.16) = 6.12, p = .035$]. ARI dose did not significantly alter larger-reinforcer choice at the session-wide level (the white bars in Figure 11a are not significantly different from one another). In visually inspecting the data displayed in Figure 11a, ARI increased the number of responses for the larger reinforcer when combined with doses of $d$-AMP more than when combined with SAL. This visual inspection is most clearly seen in comparing the black bars across clusters; however, this augmentative change in larger-reinforcer choice was not statistically significant [$F(6,42) = 1.89, p = .166$].

When focusing on the last three blocks of trials (when the overall “payout” for the larger, uncertain reinforcer was lower than the overall “payout” for the smaller, certain reinforcer), the highest dose of $d$-AMP (0.56 mg/kg) increased risky choice relative to the DMSO vehicle, indicated by increases across the shading of bars in Figure 11b. This increase is further supported by a significant main effect of $d$-AMP dose (transformed with a Greenhouse-Geisser correction [$F(1.18,8.26) = 15.14, p = .003$]). ARI did not change larger-reinforcer choice in the last three blocks when administered with SAL (compare across white bars in Figure 11b). Similar to the
pattern in the data noted for larger-reinforcer choice at the session-wide level, ARI augmented changes in larger-reinforcer choice in the last three blocks when combined with $d$-AMP, over and above what either drug did alone; however, this difference was similarly not statistically significant [$F(3.29,23.04) = 1.89, p = .155$].

**Area Under the Curve (AUC)**

Consistent with the pattern seen in the data for percent larger-reinforcer choice, $d$-AMP significantly increased risky choice when AUC was calculated as a session-wide measure (Figure 12a; these data violated assumptions of sphericity and were adjusted with a Greenhouse-Geisser correction [$F(1.17, 8.16) = 13.04, p = .006$]), and for the last three blocks when larger-reinforcer choice was maladaptive (Figure 12b; [$F(2,14) = 14.58, p < .001$]). Pairwise comparisons further supported a dose-dependent increase in AUC, such that 0.56 mg/kg $d$-AMP [$M = 0.396, SD = 0.087$] significantly increased AUC relative to SAL [$M = 0.184, SD = 0.087$] and 0.3 mg/kg $d$-AMP [$M = 0.260, SD = 0.087$] when analyses were run with AUC as a session-wide measure (Figure 12a). When only looking at AUC for the last three blocks, 0.56 mg/kg ARI [$M = 0.309, SD = 0.078$] significantly increased AUC relative to SAL [$M = 0.103, SD = 0.078$] and 0.3 mg/kg $d$-AMP [$M = 0.156, SD = 0.078$] (Figure 12b).

AUC for the whole session and AUC in the last three blocks were augmented when 0.56 mg/kg $d$-AMP was combined with ARI compared to administration with the DMSO vehicle (compare difference across black bars in Figures 12a and 12b). Although these differences were not statistically significant, the patterns seen across the data for AUC replicate patterns seen for percent larger-reinforcer choice at the session-wide level and in the last three blocks.

**Indifference Points (IPs)**
There were no significant effects of either drug on indifference point, suggesting that neither drug altered the interpolated point at which both of the reinforcers would have been selected equally [ARI: $F(3,21) = 1.12, p = .363$; $d$-AMP (Greenhouse-Geisser corrected): $F(1.12, 7.82) = 3.47, p = .098$]. Figure 13 shows mean IPs across different doses of $d$-AMP as a function of each dose of ARI.

**Discounting Rate ($h$)**

There was no significant main effect of $d$-AMP dose [Greenhouse-Geisser corrected: $F(1.09, 7.64) = 2.683, p = 0.141$] or ARI dose [$F(3,21) = 0.614, p = 0.614$] on discounting rate, or a significant interaction [Greenhouse-Geisser corrected: $F(2.15,15.08) = 1.030, p = 0.386$]. This suggests that neither drug altered the rate at which probabilistic delivery of reinforcer impacts its value. Figure 14 shows discounting rate ($h$), which corresponds to the slope of the discounting functions, ranging in value from 0.21 to 1.21.

**Win-Stay and Lose-Shift Ratios**

In measures used to detect sensitivity to reinforcer delivery (win-stay) or loss-aversion (lose-shift), there were no significant differences following $d$-AMP (Figure 15a: win-stay [$F(2,12) = 0.198, p = 0.823$] or Figure 15b: lose-shift [$F(2,14) = 1.326, p = 0.297$]) or ARI administration (Figure 15a: win-stay [$F(3,18) = 0.657, p = 0.589$] or Figure 15b: lose-shift [$F(3,21) = 0.771, p = 0.523$]).

**Percent-Change from $d$-AMP Administration with Vehicle for Larger-Reinforcer Choice in Blocks 3-5**

When examining how effects of $d$-AMP were changed as a result of combination with ARI (e.g., the interaction between $d$-AMP and ARI), ARI increased the number of responses for the larger, uncertain option in the last three blocks of trials beyond how $d$-AMP altered choice.
alone. All bars in Figure 16 fall above the x-axis (the “zero” line, or how each dose of \(d\)-AMP affects larger-reinforcer choice in the last three blocks of trials when combined with the DMSO vehicle). This suggests an interaction between the two drugs, such that although ARI did not affect choice in isolation, it amplified changes in choice when combined with \(d\)-AMP, resulting in a level of risky choice that was not seen when either drug was administered independently.

**Discussion**

Consistent with results from Experiment 1, larger-reinforcer choice systematically declined as a function of decreasing probabilities of delivery during all non-drug conditions, once again demonstrating that choice was sensitive to the programmed contingencies of the procedure. The increase in percent larger-reinforcer choice in the last three blocks seen in Experiment 1 was replicated in Experiment 2 without the loss of control by contingencies in the first block. It is unclear whether the change in control by the contingencies in the first block was responding was due to prolonged exposure to the contingencies and probability-discounting procedure, maturation, or another cause.

When looking at how \(d\)-AMP by itself influenced probability discounting, percent larger-reinforcer choice increased when examining block-by-block differences, the session as a whole, and the last three blocks. These results were supported by increases in AUC (across the session and within the last three blocks). The increases in risky choice seen in this study are consistent with existing data across a variety of dependent measures and strains of rats, thereby contributing to the generality of these data (Mai et al., 2015; Ozga-Hess & Anderson, 2021; St. Onge & Floresco, 2009; St. Onge et al., 2010).

When the two drugs were combined in Experiment 2, a significant ARI x \(d\)-AMP interaction and a significant ARI x \(d\)-AMP x block interaction for percent-larger reinforcer
choice suggested that these two drugs may have combined effects on choice beyond effects of either drug independently. Despite the non-significant analyses for other dependent variables for risky choice (e.g., examining how ARI augmented changes in AUC for the session and in the last three blocks following $d$-AMP), visual inspection of these data may suggest an interactive effect of these two drugs, such that ARI appeared to alter the extent to which $d$-AMP increased risky choice. Furthermore, sometimes small changes can be socially significant in clinical settings, despite not being statistically significant. For example, elopement (i.e., moving out of a designated area without permission or supervision) is a response class that could be considered risky and could have potentially catastrophic outcomes. Even small increases in the frequency of this potentially risky behavior might result in injury to the individual (e.g., running away when near a busy street). Depending on the topography of the “risky” behavior made by the individual, even small increases in behavior could become incredibly impactful.

The increase in percent larger-reinforcer choice is further supported by examining percent-change from $d$-AMP administration with the DMSO vehicle for number of responses for the larger-reinforcer in the last three blocks of trials. All data fall above the x-axis indicating an increase in number of responses for the larger reinforcer. It is conceded that there is a high degree of variability in the data for the interaction between ARI and $d$-AMP; however, when considering these data in conjunction with additional visual inspection across many other dependent variables (i.e., larger-reinforcer choice and AUC, both for the whole session and for the last three blocks), the trends and patterns in the data highlight a potential relation that could be further investigated and clarified. Further research should be devoted to understanding how various doses of these two drugs together influence risky choice. Despite the prevalence of polypharmacy in the treatment of various diagnoses, including comorbid ASD and ADHD, there
is a glaring absence of studies investigating how these various drugs interact and impact behavior. This study aimed to address a small component of the larger problem by examining how ARI and d-AMP alter risky choice on a probability-discounting paradigm.

**Dopamine and risky choice**

Dopamine has been implicated for its effects on responding for rewards and can be split into families of D₁ and D₂ subtypes. The D₂ receptor, particularly, has been shown to alter behaviors associated with heightened impulsivity and risk-taking. ARI is a partial dopamine agonist, primarily acting on D₂ receptors. d-AMP increases the release of dopamine into the synapse, where the neurotransmitter can then bind to either family of receptor (Azzaro & Lucci, 1987). St. Onge & Floresco (2009) have further detailed the impacts of stimulation or blockade of different dopamine receptors, noting that activation of D₁ and D₂ receptors increased risky choice on a probability-discounting task, while blockade of these receptors increased risk-aversion. Furthermore, Verharen et al. (2019) found that activation of D₁ and D₂ receptors had complementary effects on value-based learning during a probability reversal task. Given the convergent dopaminergic action of d-AMP and ARI, in combination with the divergent receptor family affinity across the two drugs, it may be fruitful to identify precise receptor activation when these drugs are administered together.

Recent research has investigated the extent to which changes in dopamine can increase during the anticipation of reward delivery (Kayser, 2019) and in the presence of arbitrary cues that acquire salience following pairings with the delivery of uncertain rewards (Zack et al., 2020). Research has shown that when rats were exposed to long periods of uncertain consequences within operant-choice paradigms, rats became sensitized to effects of dopaminergic drugs (Fugariu et al. 2020, Zack et al. 2014, Zeeb et al. 2017). This may be a
potential mechanism for shifts in responding over time. The summation of these findings may suggest that merely the stimulus conditions in which probabilistic reinforcement is delivered may elicit dopaminergic action in and of itself. Additionally, it is possible that physiological changes following dopaminergic action may come to function as conditioned reinforcers that maintain responding for uncertain programmed reinforcers (Zack et al., 2020). Given that responses that are intermittently reinforced are more resistant to extinction (see Kimble, 1961 for a review), the establishment of conditioned reinforcers (i.e., the presence of cues and the subsequent elicited dopaminergic response) may inadvertently prolong reinforcement conditions. More research is needed to investigate how dopaminergic responses to anticipatory cues develop (i.e., why might cues associated with uncertain rewards be reinforcing), whether the establishment and presence of cues associated with uncertain rewards increase risky choice, and how differential dopaminergic responses for cues versus reward delivery may correlate with changes in risky choice.

**d-AMP and Risky Choice**

Dopamine is increased following the administration of d-AMP, thereby increasing the opportunity for dopamine to bind at postsynaptic dopamine receptors (Calipari & Ferris, 2013). There is abundant literature on the different ways that d-AMP influences impulsive choice and delay discounting (see de Wit & Mitchell, 2010 for a review); however, the literature on how d-AMP influences risky choice and probability discounting is not as clear cut. Ozga-Hess & Anderson (2019) examined differential effects of various doses of d-AMP across two different strains of rats, finding that low doses of d-AMP increased risky choice on a probability-discounting task regardless of strain. Contradicting these results, d-AMP had no effect on risky choice in the rat gambling task (an animal laboratory version of the aforementioned Iowa
Gambling Task; Bellés et al, 2023). In light of these inconsistent findings, more research is needed to further investigate how d-AMP influences risky choice across different procedures, and whether changes in risky choice are consistent when d-AMP is administered in isolation or in combination with other medications.

**ARI and Risky Choice**

The dopaminergic mechanism of ARI, particularly at the D₂ and D₃ receptors, has been posited to play a role in changes in choice; however, the existing literature has not reached an agreement about the extent to which behavior does change. Similar to differences mentioned with d-AMP, studies have shown mixed effects across different impulsive choice tasks following ARI administration, regardless of baseline dopaminergic tone (decreased response latency on the rat gambling task and increased impulsive choice on delay-discounting task in Bellés et al, 2023; increased response latency on the five-choice-serial-response task in Besson et al., 2009). Conversely, no differences were noted for risky choice on the rat gambling task. St. Onge and Floresco (2009) demonstrated that activation of D₁ and D₂ receptors may increase risky choice on the rat gambling task, while activation of D₃ receptors may decrease risky choice. Given that ARI binds to presynaptic and postsynaptic D₂ receptors and D₃ receptors (having both agonistic and antagonistic activity), the simultaneous activation of both receptor types may result in competitive effects that result in the non-significant effects seen within Experiments 1 and 2. No known studies have investigated effects of ARI on other procedures to assess risky choice (e.g., probability discounting). Taking these results together with evidence that ARI has the capacity to act on both dopamine and serotonin receptors (as well as receptors for other neurotransmitters, e.g., histamine, adrenergic alpha; Sumiyoshi et al., 2008), it is unclear to what extent changes in behavior are connected to changes in dopamine, serotonin, or both. This unanswered question
warrants further research to elucidate the neurochemical mechanism(s) contributing to changes in risky choice.

**General Discussion**

Risk taking and avoidance has been investigated with individuals with ADHD and ASD, finding that individuals with ADHD tend to be more risk seeking (see Pollack et al., 2019 for a review) while individuals with ASD may be more fearful of failure and negative outcomes (South et al., 2011; South et al., 2014). Pollack et al., (2019) discuss the different “real-life” contexts in which risk-taking behavior manifests for individuals with ADHD, such as driving, gambling, sexual behavior, and delinquency, while also acknowledging the limitations of laboratory procedures designed to study risk-related behavior. Research on these types of behavior with ASD have been largely limited to contrived procedures in which risky behavior is not topographically or functionally similar to risks taken in real-life situations. Even more pressing, the degree to which risky behavior (whether contrived or naturalistic) changes following administration of various medications used for the management of ASD is crucial to ensuring that psychiatric interventions are not countertherapeutic.

Polypharmacy as a clinical practice has increased in prevalence since the year 2000, impacting a number of Americans every year, including individuals with intellectual and developmental disabilities (Valenza et al., 2017). This issue is estimated to have cost US health insurance companies billions of dollars annually. Considering the numerous medical conditions that prescribers treat, it is unreasonable to expect the selection of medications, in isolation or in combination, to account for every physical side effect. Furthermore, when multiple prescribed medications have the potential to negatively impact behavior, it would be prudent for physicians to have an understanding of the interaction between the medications prior to prescribing them.
Although medications can be prescribed *pro re nata* (i.e., PRN or “take as needed”), prescription drugs, when taken as directed, are often used chronically (Mayo Clinic, 2023a,b). Within the current study, both ARI and d-AMP were administered acutely, thus the development of tolerance to the doses used was less likely than if the doses were administered chronically. Further research is needed to investigate how choice changes following administration of these medications on a chronic basis, as well as the intermittent use of one of the medications intermittently to mimic PRN use. Furthermore, medication adherence is a prevalent problem for both physiologically directed and psychotropic medications, and is even more prevalent when more than one medication needs to be taken (Chatoo & Lee, 2022). By investigating inconsistent administration of chronic medications (i.e., low medication compliance, missed doses, drug holidays), researchers can further understand how choice may change following the omission, and subsequent renewal, of medication.

Behavioral interventions for individuals with intellectual and developmental disabilities often do not exist in isolation, but rather are implemented in conjunction with other treatments. Multidisciplinary teams bring together helping professionals with different training histories and scopes of competence to address the multifaceted needs of their patients (Frye, 2022). Understanding how behavior may change as a function of different medication combinations may contribute to the breadth of knowledge and best practices for such teams when making treatment decisions. Furthermore, knowing behavioral effects of medications or medication combinations can help to pinpoint whether changes in behavior are related to this medication change or other stimulus conditions altogether. Lastly, in tacting behavioral phenomena that arise following the administration of “drug cocktails,” professionals may give greater pause in prescribing additional medications to treat side effects when they arise and may instead begin to
shift to prescribing a different medication with a similar function but fewer side effects as newer medications are developing.

**Limitations and Future Directions**

Between Experiments 1 and 2, the range of percent larger-reinforcer choice to determine stability of behavior before drug administration days shifted for two of the rats. Additionally, the loss of control in the first block of trials following ARI administration was not replicated in Experiment 2. Research has shown that choice responding, both delayed (Aparicio et al., 2015) and probabilistic (Ozga-Hess & Anderson, 2021), may not be static, but rather may shift over time following exposure to contingencies. In the case of this experiment, it is unclear whether the shift in baseline responding was due to prolonged exposure to the discounting procedure, prolonged exposure to ARI, or due to the order with which drugs were administered (i.e., doses of ARI were interspersed with doses of d-AMP, according to the flow chart in Figure 8). This is an empirical question which warrants further study, particularly if such research may bring about the advent of behavioral interventions to reduce maladaptive choice following deliberate manipulations of reinforcement history.

The dependent variables used within the current study were selected based on the standards within the literature on probability and delay discounting. As mentioned in the procedural description, within a probability-discounting procedure, choice for the larger, uncertain reinforcer was advantageous in the first two session blocks, and disadvantageous in the last three blocks. Compared to delay-discounting procedures, it is always advantageous to choose the larger, later reinforcer across all session blocks. Because of this, dependent measures for probability discounting that have been derived from delay-discounting procedures and that are based on the entire sessions (IPs, $h$ values) may not be as sensitive to risky choice compared to
block-by-block measures. Additionally, research has shown that within-subject variability on probability-discounting procedures may be a byproduct of sampling response options (i.e., “exploratory behavior”; Rojas et al., 2022). Future work could be devoted to developing means of assessing behavior on a more molecular level, such as analyzing the slope of discounting functions solely for the last three blocks. Additionally, adapting a procedure that allows for adequate sampling of reinforcement contingencies such that behavior is more reliably controlled by the probability of reinforcer delivery rather than novelty may increase the validity of conclusions drawn from such experimental procedures.

Other variables, such as reinforcer magnitude, could also be manipulated, particularly with the possibility of ARI altering ability to discriminate (i.e., flattening of discounting functions). Natsheh et al. (2021) found that D₂/D₃ receptor activation in rats may alter choice based on incentive value, potentially implicating the role of reinforcer magnitude for choice. Additionally, research has shown that a descending probability schedule may increase risky choice compared to an ascending schedule (Yates et al., 2016). Manipulating these procedural variables may affect risky choice, as well as drug effects on these responses.

Although dopamine has been at the forefront of research on choice and decision making (e.g., dopamine is colloquially described as being a “reward neurotransmitter”; Juárez Olguín et al., 2016), it is unclear whether effects of ARI on d-AMP are due to the activation of D₂ family receptors or activation of multiple different types of neurotransmitter cites. Recall that ARI operates on multiple different monoamine receptors, including serotonin. Serotonin has also been implicated for its effects on behavior, including delayed and probabilistic choice (Homberg, 2012). Additionally, research has shown that depletion of tryptophan (from which serotonin is synthesized) can hinder learning related to aversive outcomes (Tanaka et al., 2009), and
serotonin levels have been associated with differences in reward prediction (Tanaka et al., 2007). Future research could be devoted to the interaction between the activation or blockade of multiple neurotransmitter types.

The present study was limited to the use of male Sprague-Dawley rats as subjects. The diagnostic criteria for ASD (Werling & Geschwind, 2014) and ADHD (Mowlem, 2019) were based on behavioral presentation in boys, which may impact the extent to which these diagnoses are diagnosed in females. Some preclinical research suggests that delay discounting and probability discounting may be sex-dependent (e.g., Eubig et al., 2014; Íbias & Nazarian, 2020; Smethells et al., 2016) or may occur differentially across various strains of rats (Anderson & Diller, 2010; Anderson & Woolverton, 2005; Hamilton et al., 2014; Huskinson et al., 2012; Oinio, 2022; Thomas et al., 2017). Studies have shown that different rat strains, Lewis and Fischer 344, differ from one another during baseline for delay discounting (impulsive choice). This may indicate that there are variations in biology, like dopamine or serotonin transmission, between the two strains that may differentially impact certain types of decision-making.

However, there is no known research on how strains of different strains of animals may contribute to differences in probability discounting. Furthermore, acute d-AMP had differential effects for impulsive choice based on baseline levels of responding (e.g., more responses for the larger reinforcer in baseline may lead to different effects of drug relative to fewer responses for the larger reinforcer in baseline; Hand et al., 2009; Huskinson et al., 2012). Future research could investigate how the combination of ARI and d-AMP may interact with differences in sex, strain, or neurotransmitter activity (e.g., deficits in dopamine versus serotonin) to increase our understanding of neurochemical influences on choice.

Summary and Conclusions
In summary, \( d \)-AMP dose-dependently increased risky choice across various dependent variables (e.g., session-wide LRC, LRC in the last three blocks, and AUC). Administration with ARI resulted in an even larger increase in relevant dependent variables, especially choice for the larger reinforcer during the last three blocks of trials, when larger-reinforcer delivery was not guaranteed. This work supports the existing literature on effects of \( d \)-AMP on risky choice, suggests a potential relation between ARI administration and risky choice, and demonstrates an interaction between the drugs that increases risky choice. Further work should address how procedural manipulations (i.e., probability ranges, reinforcer magnitude, order of probability presentation), chronic drug administration, sex differences, and strain differences influence risky choice and dopamine’s effects on this type of decision-making. Further research is necessary to better understand how changes to the D\(_2\) family of receptors affect choice (independently or in conjunction with other neurotransmitters), particularly within contexts of multiple psychotropic prescription use. In doing such, we may have a better understanding of how these drugs interact to influence choice for clinical populations, such as those with comorbid ASD and ADHD.
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Figure 1

*Mean Percent Larger-Reinforcer Choice as a Function of Probability of Delivery During the Last Five Sessions of Baseline*

*Note.* Error bars indicate +/- one standard error of the mean.
**Figure 2**

*Mean Percent Larger-Reinforcer Choice as a Function of Probability of Delivery During Experiment 1*

*Note.* “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean. * represent a statistically significant difference from the DMSO vehicle (*p* < .05). Higher levels of percent larger-reinforcer choice indicate more risky choice.
Figure 3a
Mean Percent Larger-Reinforcer Choice in the Whole Session as a Function of ARI Dose During Experiment 1

Figure 3b
Mean Percent Larger-Reinforcer Choice in the Last Three Blocks as a Function of ARI Dose During Experiment 1

Note. “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean. * represents a statistically significant difference at $p < .05$. Maximum number of responses for the larger reinforcer in the session was 40 and for the last three blocks was 24.
**Figure 4a**
*Mean AUC for the Session as a Function of ARI Dose During Experiment 1*

![Graph showing mean AUC for the session as a function of ARI dose.](chart1.png)

*(n = 8)*

**Figure 4b**
*Mean AUC for the Last Three Blocks as a Function of ARI Dose During Experiment 1*

![Graph showing mean AUC for the last three blocks as a function of ARI dose.](chart2.png)

*(n = 8)*

*Note.* “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean. * represents a statistically significant difference at $p < .05$, and ** represents a statistically significant difference at $p < .01$. 
Figure 5
Mean Indifference Point as a Function of ARI Dose During Experiment 1

Note. “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean. * represents a statistically significant difference at $p < .05$, and ** represents a statistically significant difference at $p < .01$. 

(n = 8)
Figure 6
*Mean Discounting Rate (h) as a Function of ARI Dose During Experiment 1*

![Graph showing the relationship between ARI dose (mg/kg) and discounting rate (h). The graph indicates a decrease in discounting rate as ARI dose increases.](image)

Note. “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean.
**Figure 7a**
Mean Win-Stay Ratio as a Function of ARI Dose During Experiment 1

![Graph showing mean win-stay ratio as a function of ARI dose.](image)

**Figure 7b**
Mean Lose-Shift Ratio as a Function of ARI Dose During Experiment 1

![Graph showing mean lose-shift ratio as a function of ARI dose.](image)

Note. “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean. * represents a statistically significant difference at $p < .05$, and ** represents a statistically significant difference at $p < .01$. 
Figure 8
Injection Combinations in Experiment 2

Note. ARI = aripiprazole, d-AMP = d-amphetamine, DMSO = dimethyl sulfoxide (vehicle for aripiprazole), SAL = saline (vehicle for d-AMP). Each combination was tested at least twice for each rat.
Figures 9a – 9d

Mean Percent Larger-Reinforcer Choice in the Last Three Blocks Across Doses of d-AMP as a Function of ARI Dose During Experiment 2

A

B

C

D

Note. “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean. * represents a statistically significant difference at $p < .05$, and ** represents a statistically significant difference at $p < .01$. 
Figures 10a – 10c
Mean Percent Larger-Reinforcer Choice in the Last Three Blocks Across Doses of d-AMP as a Function of ARI Dose During Experiment 2

Note. “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean.
Figure 11a
Mean Number of Responses for the Larger-Reinforcer Choice Across the Session Across Doses of d-AMP as a Function of ARI Dose During Experiment 2

![Graph showing mean number of responses for the larger-reinforcer choice across the session across doses of d-AMP as a function of ARI dose during Experiment 2. The graph includes data for DMSO (VEH), 0.3 mg/kg d-AMP, 0.56 mg/kg d-AMP, and 10.0 mg/kg ARI. Error bars indicate +/- one standard error of the mean. * represents a statistically significant difference at p < .05, and ** represents a statistically significant difference at p < .01. Maximum number of responses for the larger reinforcer in the session was 40 and for the last three blocks was 24.]

Figure 11b
Mean Number of Responses for the Larger-Reinforcer Choice In the Last Three Blocks Across Doses of d-AMP as a Function of ARI Dose During Experiment 2

![Graph showing mean number of responses for the larger-reinforcer choice in the last three blocks across doses of d-AMP as a function of ARI dose during Experiment 2. The graph includes data for DMSO (VEH), 0.3 mg/kg d-AMP, 0.56 mg/kg d-AMP, and 10.0 mg/kg ARI. Error bars indicate +/- one standard error of the mean. * represents a statistically significant difference at p < .05, and ** represents a statistically significant difference at p < .01. Maximum number of responses for the larger reinforcer in the session was 40 and for the last three blocks was 24.]

Note. “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean. * represents a statistically significant difference at p < .05, and ** represents a statistically significant difference at p < .01. Maximum number of responses for the larger reinforcer in the session was 40 and for the last three blocks was 24.
Figure 12a
*Mean AUC for the Session Across Doses of d-AMP as a Function of ARI Dose During Experiment 2*

![Graph showing AUC for the Session](image)

**Figure 12b**
*Mean AUC for the Last Three Blocks Across Doses of d-AMP as a Function of ARI Dose During Experiment 2*

![Graph showing AUC for the Last Three Blocks](image)

**Note.** “DMSO” corresponds to dimethyl sulfoxide vehicle and error bars indicate +/- one standard error of the mean. * represents a statistically significant difference at $p < .05$, and ** represents a statistically significant difference at $p < .01$. 
Figure 13

*Mean Indifference Point Across Doses of d-AMP as a Function of ARI Dose During Experiment 2*

Note. Error bars indicate +/- one standard error of the mean
Figure 14

Mean Discounting Rate (h) Across Doses of d-AMP as a Function of ARI Dose During Experiment 2

![Graph showing discounting rate across doses of d-AMP as a function of ARI dose.]

Note. Error bars indicate +/- one standard error of the mean.
Figure 15a

*Mean Win-Stay Ratios Across Doses of d-AMP as a Function of ARI Dose During Experiment 2*

![Bar graph showing mean win-stay ratios across doses of d-AMP as a function of ARI dose.](image)

**Note.** Error bars indicate +/- one standard error of the mean.

Figure 15b

*Mean Lose-Shift Ratios Across Doses of d-AMP as a Function of ARI Dose During Experiment 2*

![Bar graph showing mean lose-shift ratios across doses of d-AMP as a function of ARI dose.](image)

**Note.** Error bars indicate +/- one standard error of the mean.
Figure 16

Percent Change for Larger-Reinforcer Choice in the Last Three Blocks from d-AMP Administration with DMSO as a Function of ARI Administration

Note. Error bars indicate +/- one standard error of the mean.