**Title:** MDMA impairs response to water intake in healthy volunteers

**Author List:** Matthew J. Baggott¹, Kathleen J. Garrison², Jeremy R. Coyle³, Gantt P. Galloway², Allan J. Barnes⁴, Marilyn A. Huestis⁴, and John E. Mendelson²

¹San Francisco, California  
²Addiction and Pharmacology Research Laboratory, California Pacific Medical Center Research Institute, San Francisco, California  
³Division of Biostatistics, School of Public Health, University of California, Berkeley, California  
⁴Chemistry and Drug Metabolism, IRP, National Institute on Drug Abuse, NIH

**Corresponding Author’s Name:** Matthew J. Baggott, PhD  
**Contact Information:** matthew@baggott.net, phone (650) 716-4753

**Abstract:** 150 words

Hyponatremia is a serious complication of 3,4-methylenedioxymethamphetamine (MDMA) use. We investigated potential mechanisms in two double-blind, placebo-controlled studies. In study 1, healthy drug-experienced volunteers received MDMA or placebo alone and in combination with the alpha-1 adrenergic inverse agonist prazosin, used as a positive control to release antidiuretic hormone (ADH). In study 2, volunteers received MDMA or placebo followed by standardized water intake. MDMA lowered serum sodium, but did not increase ADH or copeptin, although the control prazosin did increase ADH. Water loading reduced serum sodium more after MDMA than after placebo. There was a trend for women to have lower baseline serum sodium than men, but there were no significant interactions with drug condition. Combining studies, MDMA potentiated the ability of water to lower serum sodium. Thus, while MDMA lowers serum sodium and potentiates effects of water intake on serum sodium, ADH may not be the mechanism of these changes.

**INTRODUCTION**

3,4-Methylenedioxymethamphetamine (MDMA, commonly referred to as ‘ecstasy’) is a widely used recreational drug. In the United States in 2013, reported lifetime/previous 30-day MDMA use was 6.8%/0.3% for persons aged 12 and older (NSDUH). Hyponatremia, defined as serum sodium concentrations of less than 135 mEq/L, is a potentially serious MDMA complication. Many published case reports document the significant morbidity and mortality of MDMA-related hyponatremia [1-20]. Symptomatic hyponatremia results from passive flow of water into cells, which can cause cerebral edema and may result in brain stem herniation. Clinical manifestations
include nausea, vomiting, headache, and mental status changes. In severe cases, hyponatremia may lead to seizures, coma, and death.

Hyponatremia after MDMA use is thought to involve a combination syndrome of inappropriate antidiuretic hormone secretion (SIADH) and increased hypotonic fluid intake. However, the relative roles of ADH versus fluid intake remain unclear. ADH normally is secreted when effective circulating blood volume is decreased. SIADH is marked by increased secretion of ADH despite normal circulating blood volume, resulting in plasma hyponatremia and hypo-osmolality along with urine hyperosmolality. Increased secretion of ADH has been documented in some case reports of MDMA-related hyponatremia [2, 3, 10, 12, 17, 18]. In other cases, inappropriately high urine osmolality in the setting of low serum osmolality provides additional evidence for elevated ADH [reviewed in 17]. Of note, in these case reports, there is an apparent lack of a dose-response relationship.

Controlled studies found that MDMA (and its metabolites) may induce ADH release. Henry et al. [21] administered 40 mg MDMA to eight males and reported an acute increase in ADH accompanied by a small decrease in serum sodium and an increase in urine osmolality [21-24]. Dumont et al. [25] administered 100 mg MDMA to 9 males and 7 females volunteers and saw serum sodium changes similar in magnitude to those seen by Henry and colleagues despite the considerable difference in dose. This suggests MDMA may not linearly increase plasma ADH. Consistent with this possibility, plasma MDMA and plasma ADH concentrations negatively correlated at 1 hour in the dataset of Henry and colleagues, which is the opposite of what would be predicted if MDMA induced SIADH. This lack of relationship may due to MDMA metabolites such as HMMA contributing to ADH release, as has been shown in rat hypothalamus in vitro [21-24]. A study of ecstasy users by Aitchison et al. [26] found genetic polymorphisms predicted low CYP2D6 or COMT enzyme activities were associated with greater MDMA-induced lowering of plasma sodium. This again is consistent with a role for metabolites.

In addition, the relationship between MDMA and ADH concentrations may be obscured due to the brief half-life of ADH [27, 28]. Copeptin, the C-terminal part of the ADH precursor preprovasopressin, was proposed as a biological proxy for ADH because it is released as a cofactor with ADH and has a longer half-life [29]. Simmler, Hysek, and Liechti [30] reported that 120 mg MDMA elevated plasma copeptin at 60 and 120 min compared with placebo in women but not in men. Wolff et al. [31] prospectively compared dance club attendees who went on to use MDMA with those who did not and detected significant differences in plasma and urine osmolality but not significant differences in ADH when MDMA users were compared to non-users. Taken together, this literature shows modest and inconsistent effects of MDMA on ADH levels.

Alternatively, rather than directly increasing ADH, MDMA-related hyponatremia may be secondary to some other pathophysiology. This includes hypothetical effects on gastrointestinal tract motility [12] or on renal collecting tubule functioning. Drugs including fluoxetine, oxcarbazepine, and carbamazepine were reported to induce hyponatremia without a concomitant increase in ADH [32, 33]. Fluoxetine was further
shown to increase expression of aquaporin 2 channels in the inner medullary collecting duct, increasing water reabsorption independent of ADH [34].

Hyponatremia after MDMA also likely has behavioral risk factors. The sudden historic appearance of MDMA-related hyponatremia strongly suggests a behavioral component [19]. MDMA-related hyponatremia was not reported until 1993, after harm reduction efforts began to recommend water consumption in an attempt to reduce risks of exercise-related dehydration and hyperthermia. In some hyponatremia case reports, witnesses reported that the individual consumed large amounts of water [4, 7, 13, 15, 18, 19, 35]. Thus, ecstasy-related hyponatremia may be partially due to erroneous user beliefs that water consumption reduces ecstasy toxicity.

There is a strong gender imbalance in MDMA-related hyponatremia. The vast majority of MDMA-related cases involve females who are less than 30 years-old and who ingested a single dose of ecstasy [2]. In contrast, most other syndromes of MDMA-related toxicity predominantly involve males. The high prevalence of females in MDMA-related hyponatremia is also seen in hyponatremia from other causes [e.g., 34, 36-38]. An elevated risk of hyponatremia symptoms in women is partly explained by the inhibitory effects of estrogen on brain Na+-KATPase, which elevates risk of cerebral edema [39]. Lower body weight and decreased muscle mass in females are also risk factors [12]. Sex differences in MDMA effects have been reported in Sprague-Dawley [40-42] and Wistar rats [43], which can at least in part be attributed to sex differences in MDMA pharmacokinetics [41]. Less is known about possible gender differences in MDMA pharmacokinetics in humans [44] and whether these contribute to the disorder.

We sought to investigate the mechanisms of MDMA-induced hyponatremia in two controlled studies with healthy, MDMA-experienced volunteers. In study 1, we used the alpha-1 adrenergic inverse agonist prazosin as a positive control to stimulate ADH release by decreasing blood pressure. We sought to test whether MDMA would increase ADH and whether this would be correlated with serum sodium decreases. In study 2, we investigated the effects of water loading on indices of hydration. We hypothesized that MDMA would increase the effects of water loading on serum sodium.

Results:

Study 1 included sixteen (eight male and eight female) participants, ages 26.6 ± 1.8 years (mean ± SEM; range: 18-42). Participants drank 1213 ± 76 ml (mean ± SEM) water in the 8 h following MDMA administration. Water intake did not differ by condition, body weight, or gender.

MDMA and metabolites. Pharmacokinetics of MDMA and metabolites are summarized in Figure 1 and Table 1. There were no significant effects of gender or condition (i.e., prazosin pretreatment) on MDMA kinetics.

ADH. Prazosin but not MDMA increased ADH (Figure 2). In a model predicting maximum log_{10}-transformed serum ADH levels with condition and gender fixed effects and participant as a random effect, there was a significant effect of condition on ADH
(F_{3,45} = 5.68, p = 0.002) but not gender (p = 0.11). Both prazosin conditions increased ADH compared to placebo (Prazosin alone: z = 3.46, p = 0.002; Prazosin with MDMA: z = 3.22, p = 0.004). While a few (male) participants appeared to have elevations in ADH at 1 h after MDMA, this condition was not significantly different from placebo in our model (z = 1.21, p = 0.589). Eight of 448 ADH samples were either not collected or not analyzable.

Serum sodium. Both MDMA conditions decreased serum sodium (Figure 3, top). In a model predicting minimum serum sodium concentration using condition and gender as fixed effects and participant as a random effect, there were effects of condition (F_{3,357} = 8.44, p < 0.0001) and gender (F_{1,14} = 5.913, p = 0.0291) but no interaction. MDMA alone (t_{357} = -4.05, p = 0.0001) or in combination with prazosin (t_{357} = -3.50, p = 0.0005) lowered sodium compared to placebo. Prazosin did not affect serum sodium. Females had lower minimum serum sodium than males (t_{14} = -2.43, p = 0.029). However, this did not appear to be a drug effect and was visible in their baseline measures. Eight of 448 serum sodium samples were not collected or not analyzable.

Relationships between variables. We did not detect any significant relationship between ADH and the decreases in serum sodium seen after MDMA. In fact, individuals with the lower serum sodium generally had lower ADH, as if ADH were functioning normally and suppressed in these individuals. Figure 4 provides a scatterplot of all ADH and serum sodium values collected after drug administration in the MDMA alone condition. We saw no evidence that individual variability in pharmacokinetics influenced serum sodium: Peak MDMA and HMMA concentrations (and their interaction) also did not appear to predict significantly serum sodium decreases when included in a model that already contained drug condition.

Study 2 included twelve (six male and six female) participants, ages 28.6± 1.9 years; range: 21-40). It differed from the first study in that participants in all conditions underwent oral water loading after an inpatient stay with standardized sodium and fluid intake. Females were tested during the follicular phase of their menstrual cycles. Two participants vomited within 15 min of completing oral water loading during their MDMA conditions; these data are excluded from analysis. Study procedures were otherwise well-tolerated by all participants.

ADH and copeptin. As in the previous study, we did not detect a significant effect of MDMA on ADH (Cmax: F_{1,15} = 0.113, p = 0.74). We also did not detect any effect of MDMA on copeptin (Cmax: F_{1,9} = 0.019, p = 0.89). Using data from all matching time points, there was a trend for ADH and copeptin to be correlated (Kendall's tau = 0.164, T=500, p = 0.068). Fourteen (8 from placebo) of the 120 ADH samples were not analyzable due to temperature control failures. One (from placebo, post-3-hr) of 72 copeptin samples was missing.

Serum sodium. MDMA with water loading decreased serum sodium to a greater extent than placebo with water loading (Cmin: F_{1,9} = 13.2, p = 0.005, Figure 3, bottom). Women tended to have lower baseline serum sodium, although their response to drug and water loading was not different from males. Specifically, including
gender in the model revealed a trend for females to have lower values than males (Cmin: $F_{1,10} = 3.93$, $p = 0.0755$) without a significant interaction with condition. Copeptin also predicted serum sodium, apparently independently from condition (Figure 5, right). In a model predicting serum sodium at 2 and 3 h after dosing, copeptin and condition each significantly predicted serum sodium (condition: $F_{1,32} = 12.2$, $p = 0.001$; copeptin: $F_{1,32} = 4.22$, $p = 0.048$), but there was no significant interaction. As visible in Figure 5, one female developed transient asymptomatic hyponatremia (serum sodium of 127 mmol/L) at 3 h after MDMA.

**Combined analysis.** In order to understand the interaction of MDMA and water intake, we analyzed serum sodium data from both studies combined (Figure 6). We estimated a model predicting serum sodium change from baseline using condition (i.e., the 4 combinations of drug and water loading) and time as fixed effects and participant as a random effect. This indicated there were significant effects of condition ($F_{3,278} = 19.5$, $p < 0.0001$) and time ($F_{5,278} = 16.9$, $p < 0.001$) and a significant interaction of the two ($F_{15,278} = 8.62$, $p < 0.0001$). We then tested each post-dose measurement time for the general linear null hypothesis that serum sodium after MDMA with water loading was significantly different from the sum of serum sodium changes after placebo water loading and serum sodium changes after MDMA with water restriction. This revealed significant nonadditive effects at 2 through 4 h ($z = 3.56$ to $5.19$, $p < 0.0005$). In other words, MDMA and water loading have greater ability to lower serum sodium than either intervention alone.

**Discussion**

Since its first description by Maxwell, Polkey, and Henry [5], there have been dozens of case reports of symptomatic hyponatremia in MDMA users [17, 45, 46]. Despite high rates of morbidity and mortality, there are few investigations of mechanisms of MDMA-related hyponatremia. The current manuscript describes the first controlled trial to evaluate the effect MDMA on water homeostasis in response to water loading. We find that MDMA can both lower serum sodium and exaggerate the hypnonatremic response to fluid intake. Contrary to hypotheses we find no relationship between this lowered serum sodium and either ADH or the longer-lasting co-factor copeptin. Individuals with lower serum sodium in our studies generally had lower ADH, as if there were generally normal regulation in ADH release. While this may be partly attributable to the challenges of measuring ADH, copeptin appeared to have generally the same relationship to serum sodium under placebo and MDMA conditions, even though serum sodium was shifted lower.

In line with previous findings [21, 30, 47], we detected a statistically significant decrease in serum sodium following MDMA administration compared with the placebo condition. In Study 1, both MDMA conditions (i.e., MDMA alone and MDMA with prazosin) resulted in a significant decrease in serum sodium. In Study 2, the MDMA condition was associated with a larger decrease in serum sodium following an oral water challenge compared with placebo (and water loading). Pooling data from both studies, we found evidence that the combined effects of MDMA and water loading were greater than would be predicted from these manipulations measured individually.
In contrast to the three previous studies [21, 30, 47], we were unable to detect a robust effect of MDMA on ADH levels (or the more readily detectible co-factor copeptin). In our first study, our positive control, prazosin, resulted in increased levels of ADH, while MDMA did not. In our second study, we also did not detect a significant increase in ADH or copeptin. It is possible that water loading suppressed drug-induced ADH secretion in our second study; however, this would appear inconsistent with findings from case reports. In addition, the relationship between ADH and serum sodium appeared normal after MDMA: ADH was generally lower after MDMA than placebo, as if the lowered serum sodium was leading to suppression of its release. It is worth noting that the ADH elevations reported in previous controlled MDMA studies were generally small in magnitude and did not appear dose dependent (increases seen after 40 mg in the study of Henry et al. [21] are comparable to those reported after 100 mg MDMA in the papers of Simmler et al. [30] and Dumont et al. [25]).

Variations in MDMA metabolism are expected to contribute to variability in increases in ADH since HMMA may also contribute to ADH release [21-24] and genetic polymorphisms associated with low CYP2D6 or COMT enzyme activities were associated with greater MDMA-induced lowering of plasma sodium in a study of illicit ecstasy users [26]. However, we were not able to find significant relationships between peak MDMA or HMMA concentrations in our first study.

Our results raise the possibility that MDMA may impair water balance in part (or in whole) by a mechanism that is independent of elevated ADH. There are certainly other known mechanisms by which water balance can be impaired. Drugs such as carbamazepine and oxcarbazepine are thought to potentiate the effects of ADH at the renal tubule level rather than directly altering ADH levels [48]. Oxytocin, which is released by MDMA, is believed to regulate renal water reabsorption (reviewed in [49]).

We balanced the gender of our participants and made planned comparisons for gender differences. We did detect a gender difference in serum sodium (significant in the first study and a trend in the second), but this was seen at baseline and did not appear to be drug related. MDMA did not appear to lower serum sodium more in females than males. The discrepancy between our study and past investigations may be because we administered doses that corrected for body mass, while past studies used constant mg MDMA doses, which are effectively higher in female participants with lower body masses than males. For example, Simmler et al. [30] reported that MDMA induced copeptin release in females but not males while using an average of 1.6 mg/kg MDMA in males and 2.1 mg/kg MDMA in females. It is also important to emphasize that our failure to detect gender differences in serum sodium, ADH, or copeptin does not suggest that there are no gender differences in risk of MDMA-related hyponatremia. In general, females are known to be at elevated risk of developing symptoms from hyponatremia of all causes [50, 51].

The decreases in serum sodium we and other investigators detected in controlled MDMA administration studies are on average modest, with the exception of one case of asymptomatic hyponatremia after combined MDMA and water loading we detected in Study 2. It is likely that the severe hyponatremia documented in case reports is due to a
combination of factors, including excess intake of hypotonic fluids [19]. Polydipsia observed with MDMA use in case reports may be due to hyperpyrexia, a hypothesized change in primary drive to drink, and exposure to harm reduction messages emphasizing the need to avoid dehydration [19, 52]. Unfortunately, we did not measure thirst in either of our studies.

Our research has several limitations. Both studies used single dose levels of study drugs. In our first outpatient study, participants’ hydration statuses may have varied at the start of the study. Our second inpatient study was designed to correct these limitations. Another limitation is that we did not measure self-reported thirst. It is important to establish to what extent MDMA may alter thirst or increase polydipsia [19].

In conclusion, we found that MDMA lowers serum sodium but we were not able to relate this change to ADH or copeptin. We also found that MDMA acutely exaggerates the hyponatremic effects of water, suggesting that hypotonic fluid intake is likely a risk factor for MDMA-related hyponatremia.

Materials and Methods

The current manuscript describes the effects of MDMA and water loading on plasma ADH and serum sodium. Additional self-report and computerized neurocognitive tasks measures relating to emotional effects of MDMA will be described in separate manuscripts.

Participants. We recruited healthy, MDMA-experienced individuals between the ages of 18 and 50, through newspaper and on-line advertisements and word-of-mouth. A physician determined participants to be healthy based on medical questionnaires, laboratory screenings, and a physical exam. Exclusion criteria included: DSM-IV dependence on MDMA or any other psychoactive drug (except nicotine or caffeine); desire to quit or decrease MDMA use; history of adverse reaction to study drugs; current enrollment in a drug treatment program; current supervision by the legal system; any current physical or psychiatric illness that might be complicated by the study drugs or that might impair ability to complete the study; body mass index (weight/height^2) greater than 30 or less than 18 kg/m^2; and current or recent use of any medication that might pose a risk of drug-drug interaction.

Description of Procedures or Investigations Undertaken. Both studies used a double-blind, placebo-controlled, within-subject, sequence- and gender- balanced design. We selected 1.5 mg/kg MDMA, measured as the hydrochloride salt, as an active dose. We chose a dose that would produce typical drug effects without clinically significant changes in physiological parameters or detectible harm to participants, based on past clinical studies [e.g., 53, 54-57]. Administration of MDMA or its placebo took place between 10 and 10:30 am.

Study 1 design. In four experimental sessions that were separated by at least one week, outpatient volunteers experienced the following conditions: (a) Placebo prazosin followed one hour later by placebo MDMA; (b) Placebo prazosin followed one hour later
by 1.5 mg/kg oral MDMA; (c) 1 mg oral prazosin followed one hour later by placebo MDMA; or (d) 1 mg oral prazosin followed one hour later by 1.5 mg/kg oral MDMA. The first two participants (1 male, 1 female) received two mg prazosin. However, postural hypotension, an anticipated effect of prazosin, persisted for approximately 9-11 h after MDMA. In response, we lowered the dose to 1 mg for the remaining fourteen individuals. To minimize effects of water consumption, participants were limited to drinking 1 pt (about 473 mL) or less of water each hour.

Study 2 design. In two experimental sessions that were separated by at least one week, participants were admitted into a hospital research ward on the evening before drug administration and fed standardized meals for dinner (including 500 mL water) and breakfast (≤ 500 mg sodium, finished at least 1.5 h before dosing). Volunteers experienced the following dosing conditions: (a) Placebo followed one hour later by oral water challenge; (b) 1.5 mg/kg oral MDMA followed one hour later by oral water challenge. Water challenge was performed by having participants drink 20mL/kg of water within 30 minutes. No other fluid intake was allowed until at least 6 h after MDMA/placebo administration.

Materials. MDMA was kindly provided by David Nichols, Ph.D. (Purdue University, IN). Prazosin was purchased commercially. We used opaque gelatin capsules to hold MDMA and over-encapsulate prazosin. We used lactose as placebo.

Ethics. We conducted this research according to the code of ethics established by the declaration of Helsinki as amended in Edinburgh. The California Pacific Medical Center Institutional Review Board approved the studies. MDMA and prazosin were administered under an Investigational New Drug exception for MDMA from the Food and Drug Administration. Volunteers provided written consent after being informed both orally and in writing of the study procedures.

Safety monitoring. Safety monitoring included negative urine drug screening (and, if female, negative urine test for pregnancy) immediately prior to dosing, and monitoring of vital signs until at least six h after MDMA/placebo dosing. Researchers were trained to monitor for symptoms of hyponatremia or other toxicity and were continually present for at least 8 h.

Measures. We collected blood samples for ADH and plasma sodium at baseline and 1, 2, 3, 4, 6 and 24 h after dosing. We collected urine in pooled samples before dosing, and 0-8 and 8-24 h after. We measured plasma and urine sodium (mmol/L) using Siemens Dimension RxL Max Integrated Chemistry System and determined plasma ADH concentrations with Radio Immunoassay (RIA). For sodium, the inter-assay coefficients of variation were 0.74% and 1.11% respectively at 119 mg/dL. For ADH, the lower limit of detection was 1.0 pg/mL and inter-assay and intra-assay coefficients of variation were 5.4% and 7.1% respectively. We measured copeptin in study 2 using enzyme-linked immunosorbent assay (Phoenix Pharmaceuticals, Burlingame, California). The lower limit of detection was 0.4 pmol/L, and the inter- and intra- assay coefficients of variation were less than 4%. In study 1 only, we collected blood samples to measure MDMA and its metabolites (4-hydroxy-3-methoxymethamphetamine [HMMA], 4-
hydroxy-3-methoxyamphetamine (HMA) and 3,4-methylenedioxymethamphetamine (MDA) before and 1, 2, 4, 8, 24, and 48 h after MDMA, using the method of Scheidweiler and Huestis [58].

**Statistical analysis.** We analyzed data using mixed-effects models in R [59] with drug condition as a fixed effect and participant as a random effect using a 2-tailed 0.05 level of significance. When analyses identified a main effect of drug condition, we made pairwise comparisons using Tukey’s HSD, and an additional model was made with gender included as a fixed effect, although this was regarded as exploratory given that the sample size limited statistical power. We checked the normality of error terms and log10-transformed data when errors were not normally distributed. Repeated measures were generally transformed to Emax [60] summary measures before analysis. We estimated pharmacokinetic parameters in NONMEM using a noncompartmental model using linear trapezoidal calculations and linear weighing of lambdas. Correlations were calculated using Kendall’s tau.

**Study Highlights**

**What is the current knowledge on the topic?** Hyponatremia is a rare serious complication of MDMA use. Mechanisms are incompletely understood but may sometimes involve inappropriate secretion of antidiuretic hormone (ADH).

**What question does this study address?** This study addresses the mechanisms of MDMA hyponatremia by measuring acute changes in serum sodium and ADH after intake of MDMA and solute-free water.

**What this study adds to our knowledge.** A modest oral dose of MDMA is shown to acutely impair serum sodium homeostasis after water intake.

**How this might change clinical pharmacology and therapeutics**
Clinical trials with MDMA should monitor intake of fluids, especially in females. Illicit users are routinely advised to drink lots of fluids but this advice may be wrong.

**Author Contributions**
MJB, KJG, GPG, AJB, MAH, JEM - Wrote the manuscript
MJB, JRC, GPG, MAH, JEM - Designed the research
MJB, KJG, GPG, JEM - Performed the research
MJB, JRC - Analyzed the data
AJB, MAH - Contributed new reagents/analytical tools

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**Conflict of Interest**
The authors have no conflicts of interest to declare.

REFERENCES


Table 1: Pharmacokinetic results from Study 1. Values are given as Mean ± SD. Abbreviations: AUC0–∞ area under the curve from 0 to extrapolated to infinity, CL plasma clearance, Cmax maximum plasma concentration, tmax time of maximum plasma concentration, Vz apparent volume of distribution, λz first order elimination constant, t1/2 half-life.

Figure 1: Pharmacokinetics of MDMA (black) and HMMA (grey) from Study 1 after MDMA alone or prazosin with MDMA in male and female participants

Figure 2: Antidiuretic hormone (ADH) after placebo, MDMA, prazosin, and prazosin with MDMA in Study 1

Figure 3: Serum sodium changes over time during Studies 1 (upper plot) and 2 (lower plot)

Figure 4: Relationships between Antidiuretic hormone (ADH) and serum sodium at 1, 2, and 4 h after MDMA in Study 1.

Figure 5: Relationships between Antidiuretic hormone (ADH, left), Copeptin (right), and serum sodium at 2 and 3 h after MDMA (black) or placebo (grey) in Study 2.

Figure 6: MDMA impairs serum sodium homeostasis after water loading. Plot shows effects of MDMA and water loading on serum sodium using data pooled across Studies 1 and 2.
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Placebo

MDMA

Prazosin−MDMA

Prazosin

MDMA

Placebo
Combined Study 1 & 2 Conditions

- Placebo, water loading
- Placebo, restricted water
- MDMA, water loading
- MDMA, restricted water