Title
Quench the Thirst

Journal
Biological Research For Nursing, 16(4)

ISSN
1099-8004

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Publication Date
2014-10-01

DOI
10.1177/1099800413505900

Peer reviewed

Published in final edited form as:
Biol Res Nurs. 2014 October ; 16(4): 456–466. doi:10.1177/1099800413505900.

Quench the Thirst: Lessons from Clinical Thirst Trials

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Abstract

Thirst, as a symptom, has long been considered the most prevalent clinical complaint patients voice in healthcare settings. Yet, rarely have researchers examined thirst by its correlation with physiologic factors. This review was undertaken to examine the relationships between thirst ratings and factors mediating its primary physiologic correlates: plasma osmolality (pOsm) and arginine vasopressin peptide (AVP).

Methods—A literature search was undertaken to identify clinical studies in human subjects that investigated the relationship of thirst to specific physiologic thirst-related correlates and associated thirst mediators.

Findings—The 17 studies reviewed induced thirst by hyperosmolar infusion, through water deprivation or exercise weight-loss regimens. They confirmed intact osmotic thirst drives demonstrated by positive linear relationships between thirst ratings and rising serum pOsm levels. However, the normal compensatory rises in AVP levels that followed the rises in plasma osmolality varied. Alterations in AVP response were modified by exposure to cold, physical pre-conditioning and water immersion tests. Notably, older adults reported diminished thirst ratings. Weak correlations suggest that angiotensin II may play only a minor role in thirst mediation. Atrial natriuretic hormone's inhibitory effect on thirst was inconsistent.

Conclusions—Older adults are at higher risk for profound dehydration due to sensory deficits along with failure to correct volume losses. Clinical thirst trials demonstrated that serum pOsm values were highly correlated with patients' thirst ratings, with the exception of the older adult.

Keywords

thirst; plasma osmolality; arginine vasopressin; dehydration; hypodipsia

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The symptom of unrelieved thirst is one of the most prevalent and distressful complaints patients voice in healthcare settings. Prior studies have explored the prevalence of thirst as a subjective complaint. A startling 70% of patients in the intensive care unit described having moderate-to-severe thirst (Nelson et al., 2001; Puntillo et al., 2010). Elderly patients reported escalating thirst as their heart failure worsened (Waldréus, Sjöstrand, & Hahn, 2010), and thirst burdened some terminally ill patients, even in their final days (McCann, Hall, & Groth-Juncker, 1994; Morita, Tei, Tsunoda, Inoue, & Chihara, 2001). Yet despite the persistent presence of thirst in these patients, little research has addressed the unique relationship between the subjective sensation of thirst and its network of physiologic correlates.

Can the cumulative observations from experimental studies illuminate the physiologic components of this common human complaint? Our aim in this literature review was to explore the associations between human subjective reporting of thirst and its physiologic correlates, plasma osmolality (pOsm) and arginine vasopressin peptide (AVP), and to identify factors that modify thirst.

Background

Thirst plays a key role in the regulation of body-fluid homeostasis by motivating vertebrates to seek constant supplies of water and sodium to maintain fluid balance. Thirst is activated by minute 1–2% increases in pOsm. The increased osmolality draws water from cells into the blood causing intracellular dehydration. This osmotic shift activates specific brain osmoreceptors in the hypothalamus to release AVP, or anti-diuretic hormone (ADH). The released AVP acts immediately on the kidneys to enhance the reabsorption of water to dilute the increased osmolality. Thirst is initiated when the AVP reabsorption of water fails to dilute pOsm. Osmolality, defined as the ratio of solute to water, can be altered by either an increase in solute concentration and/or a decrease in the water to solute ratio. Thus, thirst can be stimulated either by increased pOsm or marked (5–8% loss in body-fluid volume) decreases in plasma volume. In dehydration, when both increased pOsm and extracellular volume loss may occur, thirst is stimulated by a complex feedback system of inhibitory and excitatory osmoregulatory signals to restore blood flow. Central osmoreceptor neurons stimulate the release of AVP and, in the kidneys, the low-volume and pressure sensors raise circulating renin-angiotensin levels. The released angiotensin II in turn promotes the secretion of aldosterone to retain sodium and conserve water. Acting in concert, these central and peripheral signals activate specific sites in the brain to stimulate the conscious perception of thirst and drinking to restore fluid homeostasis. In reverse conditions, when fluid intake exceeds fluid loss, atrial natriuretic hormone (ANH) is released from cardiac stretch-sensitive receptors. The released ANH inhibits AVP secretion which prompts fluid diuresis and sodium excretion in the kidneys and curtails thirst (Baylis, 1987; Bourque, 2008; Stricker & Hoffinann, 2007; Szinnai et al., 2007). Thirst, therefore, is directly influenced by subtle rises in pOsm that regulate the fluid-conservatory release of AVP, the critical determinant for the central (brain) osmoregulation of thirst.

Method

Literature Search for Human Thirst Studies

We undertook a search of the literature in the PubMed and Web of Science databases to identify clinical studies published between 1990 and 2012 that investigated the relationship of thirst to specific thirst-related physiologic correlates such as pOsm and associated thirst mediators. We first searched using the following key physiologic terms: thirst, thirst mechanisms, pOsm, AVP, ADH, renin angiotensin aldosterone system, angiotensin II (A-II), and *ANH*. Next, we searched on terms related to the effect of thirst on fluid regulation: sodium appetite, water deprivation, dehydration, hypovolemia and *hypervolemia*. In addition, we searched using terms naming associated factors such as advanced age, behavioral and environmental factors as potential thirst mediators. Finally, we limited our search to studies conducted with human subjects so that the participants' thirst reports could be associated with the key physiologic correlates. This search initially yielded 1354 thirst-related studies conducted with human subjects from 1990 to December 2012. The screening process we used to identify the final selected studies is described in Figure 1.

We excluded studies from the present review if (1) the study was not a clinical trial, (2) the primary physiological correlates of thirst—pOsm and AVP levels—were not included in the analysis, (3) participant thirst reports were not quantified on a scale such as a visual analogue scale (VAS) or numeric rating scale (NRS), or (4) thirst was reported solely as a side-effect of medication or exogenous hormonal treatment. In addition, we excluded investigations of conditions related to abnormalities in vasopressin function such as sudden inappropriate secretion of antidiuretic hormone (SIADH), diabetes insipidus (DI), or cases of psychosis-related polydipsia. In cases when the same first author published similar studies on osmoregulation and thirst, we selected for review only the latest published study that met the inclusion criteria.

Evaluation of Design and Methodology Quality

We developed a grading scale to evaluate the quality of the design and methodology for each study, assigning points based on the following criteria: description of appropriate randomization procedures, blinding procedures, information about withdrawals and dropouts, one or more control or comparative groups, clear description of intervention, and validated intervention measures (Deeks et al., 2003; Jadad et al., 1996). Each criterion had a possible score of 0 to 2 (0 = absent, 1 = partially defined, 2 = clearly defined), with the highest possible total score for each article being 12. We considered studies with scores < 5 to be of low-quality design, and scores > 6 indicated a high-quality study design. The total quality score for each study design is reported in Table 1.

Results

Selected Clinical Thirst Trials

Table 1 summarizes the 17 human subject thirst and physiologic correlate trials that met the inclusion criteria for this review. Studies are listed in ascending chronological order by first author from 1991 to 2008 (we found no articles published between 2009 and 2012 that met

the inclusion criteria). Of the 17 thirst trials, 6 focused on the mediating effects of aging on the identified thirst correlates and thirst sensation.

Clinical Thirst Trial Designs

All of the thirst trials were designed as prospective studies, with 13 studies recruiting participants from pools of healthy volunteers while 4 drew from patient groups. Sample sizes ranged from 6 to 30 subjects. Seven of the trials used one-group crossover or before–after designs (Burrell, Palmer, & Baylis, 1992; Figaro & Mack, 1997; Maresh et al., 2004; O'Neill, Duggan, & Davies, 1997; E. M. Phillips, Butler, & Baylis, 1994; Thompson, Selby, & Baylis, 1991; Wazna-Wesly, Meranda, Carey, & Shenker, 1995), while two groups of volunteers participated in each of the remaining seven crossover studies (Davies, O'Neill, McLean, Catania, & Bennett, 1995; Farrell et al., 2008; Kenefick, Hazzard, Mahood, & Castellani, 2004; Merry, Ainslie, Walker, & Cotter, 2008; P. A. Phillips et al., 1993; Stachenfeld, DiPietro, Nadel, & Mack, 1997; Takamata et al., 1999). Investigators who used more than one group were able to conduct repeated-measures testing as long as there was a wash-out period to avoid carry-over of the experimental treatment. For the crossover thirst trials exploring the effect of age on thirst, researchers recruited groups of younger and older subjects (Davies et al., 1995; Farrell et al., 2008; P. A. Phillips et al., 1993; Stachenfeld et al., 1997; Takamata et al., 1999).

The researchers in two studies (Martinez-Vea, Garcia, Gaya, Rivera, & Oliver, 1992; McKenna et al., 1999) employed quasi-experimental designs. Martinez-Vea et al.(1992) divided chronic kidney disease (CKD) patients into two groups using their interdialytic weight gain (IDWG) and included a third group of healthy controls. The three groups in McKenna et al.'s (1999) study were patient survivors of hyperosmolar nonketotic coma (HONK), type II diabetic (DM) patients and nondiabetic (non-DM) controls. Both studies examined subjects who were critically or chronically ill. There was only one case–control design among the studies we reviewed, which matched the thirst perceptions of uremic patients with those of healthy volunteer controls (Argent et al., 1991).

Methods: Thirst Activation and Measurement

To study thirst sensation, investigators artificially stimulated thirst in two ways: an infusion of hypertonic saline or a series of monitored exercise-dehydration protocols. Researchers successfully used hypertonic 5% (855 mmol/l) saline in studies in the 1980s to stimulate AVP release and thirst (Baylis, 1987; Phillips, Rolls, Ledingham, Forsling, & Morton, 1985; Thompson, Burd, & Baylis, 1987). This hyperosmolar method was used in 8 of the 17 thirst trials we reviewed. Subjects received 5% saline boluses at rates that ranged from 0.05 to 0.1 ml/min/kg administered over 1–2 hr (Argent, Burrell, Goodship, Wilkinson, & Baylis, 1991; Farrell et al., 2008; Martinez-Vea et al., 1992; Thompson et al., 1991). The one exception to the administration of 5% saline was the 2.7% (462 mmol/l) saline that Davies et al. (1995) infused in their study. Hypertonic saline was also alternated with 20% mannitol (E. M. Phillips et al., 1994) or preceded by atrial natriuretic hormone (ANH) infusion or .9% (154 mmol/l) saline placebo (Burrell et al., 1992) or a 2-hr infusion of one of three ANH concentrations or .9% saline placebo (Wazna-Wesly et al., 1995).

Although 5% saline was considered the gold standard for thirst induction, the increase in pOsm could adversely affect fluid balance in patients susceptible to heart failure or liver cirrhosis. As an alternative, thirst was induced by controlled periods of water deprivation or fluid restriction. The periods of fluid restriction varied from 24 hr (P. A. Phillips et al., 1993) to 16 hr for long-term-care residents (O'Neill et al., 1997) to 8 hr for diabetic patients (McKenna et al., 1999).

In the majority of the remaining studies, thirst was activated by a variety of methods to produce approximately 2–4% losses in body weight to raise pOsm levels (Figaro & Mack, 1997; Kenefick et al., 2004; Maresh et al., 2004; Merry et al., 2008). In the remaining study, an unspecified amount of weight loss was achieved after 6 consecutive days of exercise cycles in 36°C conditions (Takamata et al.,1999). In Maresh et al.'s (2004) study, subjects underwent 4 days of treadmill exercises. Kenefick et al.(2004) induced thirst by first imposing a period of dehydration followed by controlled rehydration. After this subjects rated their thirst then exercised or stood still in cold (4°C) or temperate (27°C) conditions while blood samples were drawn. Unique to Stachenfeld et al.'s (1997) study, subjects rated their thirst after 150 min of monitored exercise, then they were immersed to the neck in tap water (called HOI [head-out-of-water immersion]) for 195 min to mimic the effect of central volume expansion.

Some investigators measured thirst intensity using a 0–10 numeric rating scale (NRS), with higher numbers meaning greater thirst intensity. This method of rating a symptom has been widely used to assess pain intensity and has construct (Downie et al., 1978; Jensen, Karoly, & Braver, 1986) and concurrent validity (Downie et al., 1978; Reading, 1980). In other studies, thirst was measured by a visual analogue system (VAS). Unlike an NRS, a VAS uses no numbers. Generally, respondents are asked to put a vertical line across a 10-cm horizontal line to indicate the intensity of a symptom, where the left side of the line means no symptom and the right side means the worst intensity of the symptom. The actual intensity of the symptom can be determined by measuring the length from the beginning of the line on the left side to the vertical line. Thirst was rated using either the VAS or NRS at specified intervals in all the studies reviewed, and the ratings were timed to coincide with the blood draws for analyses.

Thirst Ratings and Plasma Osmolality

Investigators found a significant correlation between linear increases in baseline thirst ratings and rising pOsm levels in 10 of the reviewed trials (Argent et al., 1991; Burrell et al., 1992; Davies et al., 1995; E. M. Phillips et al., 1994; Farrell et al., 2008; Figaro & Mack, 1997; Maresh et al., 2004; Martinez-Vea et al., 1992; Thompson et al., 1991; Wazna-Wesly et al., 1995). An exception to this significant association was seen in the weak correlation between pOsm and the thirst scores of O'Neill et al.'s (1997) elderly nursing patients. Despite 16 hr of dehydration, their thirst scores correlated poorly with their pOsm levels (r = 0.28, $p < 0.001$). In contrast, there was the high correlation between the thirst ratings and pOsm levels (r^2 = 0.93) in Merry et al.'s (2008) study, although the trained volunteers in the study rated their thirst higher than the untrained volunteers (4.0 ±1.5 vs. 2.7 ± 1.2, respectively, on a 1–9-point NRS, p = 0.05). Finally, in Martinez-Vea et al.'s (1992) study

the CKD patients with the higher IDWG had the highest thirst scores (p <0.005), which may be have been associated with their low pOsm thirst threshold (277.6 ± 7.6 mosm/kg)..

In contrast, there were subjects with high pOsm levels who also reported hypodipsia or low thirst scores. HONK patients were less thirsty after 8 hr of water deprivation in McKenna et al.'s (1999) study (0.8 ± 0.3 to 3.5 ± 0.8 cm, 0–10-cm VAS) than the type II diabetic group (1.0 ± 0.9 to 7.7 ± 1.6 cm) and nondiabetic controls (1.1 ± 0.5 to 7.4 ± 1.3 cm). The researchers suggested that the hypodipsia could be due to their high pOsm thirst threshold (307.7 ± 2.7 mmol/kg, p < 0.05), which was the highest among the three groups (type II diabetic: 294.3 ± 3.2 mmol/kg; control group: 296.9 ± 3.0 mmol/kg, p < .01). Hypodipsia was also present when subjects were exposed to cold temperatures in Kenefick et al.'s study (2004). Their thirst ratings dropped by 40% despite their elevated pOsm levels (p < 0.05).

Hypodipsia was also reported by older subjects in three of the studies in which dehydration-exercise methods were used to induce thirst. Older subjects had lower thirst scores than younger subjects in P. A. Phillips et al.'s study (1993; 2.4 ± 8 vs. 4.4 ± 0.5 cm, respectively, on a VAS, p < 0.05], in Stachenfeld et al.'s (1997) water-immersion study (69 ± 8 vs. 94 ± 6 mm, respectively, on a VAS, p < 0.05), and in Takamata et al.'s (1999) study (26.1 ± 9.4 v. 56.0 ± 3.2 mm, respectively on a VAS), despite having higher pOsm levels . These findings suggest that the close association between thirst and pOsm level, especially for the older adult, may be mediated by factors that include co-morbidities, the blunting effect of older age on osmoreceptors, and extreme environmental conditions.

Thirst and AVP Release

The normal positive correlation between a rising pOsm level and compensatory AVP release was demonstrated in eight thirst trials (Argent et al., 1991; Burrell et al., 1992; Figaro & Mack, 1997; Maresh et al., 2004; Martinez-Vea et al., 1992; E. M. Phillips et al., 1994; Thompson et al., 1991; Wazna-Wesly et al., 1995). In the remaining studies, multiple, often competing, factors that affected pOsm and thirst also mediated AVP release. For example, cold temperature, as an environmental mediator, reduced both thirst ratings and AVP values (66%; p < 0.05; Kenefick et al., 2004).

Older age, in particular, appears to have had an attenuating effect on thirst even when subjects had comparable AVP levels. In P. A. Phillips et al.'s (1993) study older subjects reported less thirst than the younger subjects despite similar AVP levels (6.2 ± 0.6 [younger], 6.5 ± 0.6 pmol/l [older], p < 0.001]. Nor did the AVP levels in older subjects and elderly nursing home patients demonstrate the normal baseline fluctuation in response to hypertonic saline infusion and subsequent rapid drop with drinking (O'Farrell et al., 2008; O'Neill et al.1997). Stachenfeld et al. (1997) observed a marked delay of up to 15 min among older subjects in the compensatory release of AVP, which normally occurs within 3–5 min (Geelen et al., 1984). The investigators hypothesized that this delay was due to a disassociation between the older adults' central volume sensitivity, thirst appreciation and their AVP response (Stachenfeld et al., 1997).

In other studies, subjects with elevated (McKenna et al., 1999; Merry et al., 2008), as well as depressed (Davies et al., 1995; Takamata et al., 1999), AVP levels exhibited hypodipsia.

Thus, although pOsm level is the primary determinant of AVP release, the variations in these studies suggest that multiple mechanisms inhibit and disinhibit AVP release. Investigators are only beginning to identify these mechanisms by neuroimaging through positron emissions tomography (Denton et al., 1999a; Denton et al., 1999b; Farrell et al., 2008).

Thirst and Angiotensin II or Plasma Renin Activity

Several previous studies have examined the influence of the complex enzyme– neuropeptide system that activates angiotensin II on the uremic patient's excessive thirst or hyperdipsia (Fitzsimons, 1998; Fitzsimons & Wirth, 1978; Johnson, Mann, Rascher, Johnson, & Ganten, 1981; Yamamoto et al., 1986). This unique relationship between angiotensin II (A-II) or plasma renin activity (PRA), the precursor hormone for A-II, and thirst was addressed in seven of the thirst trials that we reviewed.

In the presence of hypovolemia, or extracellular volume loss, the A-II and PRA concentrations are expected to rise. Maresh et al. (2004) found that the precursor PRA and aldosterone levels rose immediately after exercise in their dehydration study. McKenna et al.'s (1999) HONK subjects (*M* age 70.6 years) had a higher baseline rise in PRA concentration than subjects with type II diabetes and the healthy controls ($p = 0.009$), suggesting that the dehydrated HONK subjects experienced greater fluid loss. In contrast, the older subjects in three of the trials had either depressed or no change in PRA activity and aldosterone in the postdehydration phase (P. A.Phillips et al., 1993; Stachenfeld et al., 1997; Takamata et al., 1999). Investigators attributed this suppressed PRA response to declining baroreceptor sensitivity to extracellular volume losses (Stachenfeld et al., 1997; Takamata et al., 1999) and/or possibly to age-related changes in the neural pathways that instigate the perception of thirst (P. A.Phillips et al., 1993).

Although the CKD subjects in Martinez-Vea et al.'s study (1992) had higher baseline AII levels than the healthy controls (27.3 ± 8.6, 15.1± 0.4 vs. 1.3 ± 0.1, pg/ml), the researchers found no relationship between the CKD patients' A-II levels and their excessive IDWG. They concluded that this finding suggests that A-II has only a minor contributing role in uremic patients' thirst and fluid regulation. (Of note, the endogenous A-II levels of Martinez-Vea et al.'s [1992] CKD patients were 20 times lower than the A-II levels that had been required to stimulate thirst in an earlier study with normal subjects [P. A. Phillips, Rolls, Ledingham, Morton, & Forsling, 1985.]

Thirst and Atrial Natriuretic Hormone (ANH)

The anti-dipsogenic effect of the ANH infusions was explored in four of the reviewed thirst trials. In Burrell et al.'s study (1992), 60 min after ANH (2 pmol/kg/min) was infused with 5% saline (855 mmol/l NaCl), volunteers' thirst ratings were significantly reduced ($p < 0.05$) compared to their ratings with the ANH-only or placebo (150 mmol/l saline) infusion. However, in Wazna-Wesly et al.'s (1995) trial, none of the three graduated concentrations of ANH (with the highest being 5.4 pmol/kg/min—a concentration 25 times higher than normal) and 5% saline bolus had an effect on the volunteers' thirst ratings. Although the

volunteers' thirst ratings were unchanged by the ANH infusions, there was a positive correlation ($r = 0.57$, $p < 0.02$) between pOsm and ANH levels.

Two of the reviewed trials explored naturally occurring levels of ANH. The older subjects in Stachenfeld et al.'s (1997) water immersion study had ANH levels that were 3-fold higher than those of the young subjects ($p < 0.05$). Elevated ANH levels were also observed among the older subjects in P. A. Phillips et al.'s (1993) trial, even after water loading. By contrast, younger subjects' NH levels fell immediately to post deprivation levels ($p < 0.01$) after they drank water. Investigators interpreted these high ANH levels as further evidence of diminished renal clearance in aging kidneys and, perhaps, a hypersensitive response to volume loading.

Quenching Thirst

Thirst was effectively and rapidly quenched in most of the trials. Of note, decreases in thirst ratings were followed by corresponding and immediate reductions in AVP levels. Less understood is the mediating effect of hypodipsia on fluid replacement in older adults. A decrease in fluid intake was clearly demonstrated in Takamata et al.'s (1999) trial involving 6 days of exercise and heat acclimation to improve fluid regulatory function in older subjects. Older subjects failed to replenish their fluid losses during the 2-hr rehydration periods, recovering only 31% of their fluid loss on Day 1 and 34% on Day 8. In comparison, younger subjects recovered up to 56% of their fluid loss on Day 1 and 80% on Day 8. O'Neill et al. (1997) also observed inadequate fluid replacement in dehydrated elderly (age > 80 years) nursing-home residents, who had an estimated average fluid intake of 1100 ml/day, an amount far below the recommended average of 3.7 L for males weighing 70 kg males. McKenna et al. (1999) also noted that the hypodipsic HONK subjects (mean age of 70.6 years) drank less water than the DM (mean age 70.5 years) and non-DM groups (mean age 69.8 years; $p < 0.001$). The researcher suggested that the acute metabolic event experienced by HONK subjects may have precipitated a "premature aging" of their osmoreceptors that blunted their response to hypovolemia.

Figaro and Mack's (1997) study was the only one we reviewed in which the researchers examined the modifying effect of peripheral oropharyngeal receptors on regulation of fluid. When dehydrated subjects drank cool water, AVP levels fell rapidly, as expected, from 4.8 ± 0.9 to 2.7 ± 0.3 pg/ml within 5 min. However, when the same amount of water was infused via nasogastric (NG) tube, thus bypassing the oropharyngeal receptors, there was no effect on AVP levels. To rule out the confounding effect of gastric distension, investigators then allowed subjects to drink water while extracting all the ingested fluid from the stomach via NG tube. Within 5 min, AVP levels still decreased from 5.3 ± 0.4 to 4.1 ± 0.7 pg/ml ($p < 0.05$). Investigators concluded that that the oral ingestion of fluids stimulated the oropharyngeal receptors and provided sensory cues to terminate drinking by reducing thirst. Oropharyngeal metering effects may play a role in maintaining fluid homeostasis by limiting the rate of fluid intake, even in the presence of unlimited access to water. P. A. Phillips et al. (1993) observed that the act of drinking amounts of replacement fluid sufficient to inhibit AVP release occurred in young healthy subjects but not in the elderly men in their trial. They also noted that dogs had exhibited this behavior in previous experimental studies.

Thirst Trial Quality Evaluation

Most important to note in our evaluation of the quality of the designs and methodologies of the studies reviewed is that the symptom of thirst, despite being the elemental drive to seek water, has yet to be fully explored in large randomized controlled trials. However, in this core group of clinical studies, researchers have examined the sensation of thirst and its physiology. Our evaluation yielded 6 studies (35%) with scores (< 5 points) indicating low design quality and 11 studies (65%) with scores (> 6 points) indicating high-quality study designs. The majority (88%) of the clinical trials used nonprobability sampling techniques to select their study populations, rendering little control over sampling bias. Researchers described limited randomized selection processes for the study participants in only 2 of the studies. These design weaknesses and small sample sizes (6–30 subjects) severely restrict the generalizability of the study outcomes.

Only one of the high-quality studies had a single-group before-and-after design (O'Neill et al., 1997). The remaining high-quality studies tested experimental treatments using one or more control or comparison groups. In all of the studies, authors provided detailed descriptions of rigorous thirst-induction protocols that included concomitant timing of thirst ratings and blood sampling. The timing of thirst and AVP assessment was especially critical given AVP's estimated half-life of 5–6 min (Seckl, Williams, & Lightman, 1986). To track the rapid fluctuations in blood values, researchers often drew blood samples at 5–10-min intervals throughout interventional phases. One author estimated that the multiple blood draws required the extraction of approximately 250 ml of blood from each subject (P. A. Phillips et al., 1993). The loss of blood from the frequent blood draws in this and other studies may have inadvertently contributed to the overall volume depletion in subjects and affected their thirst.

Discussion

Clinical Thirst Trial Outcomes

Although these clinical trials do not present causal evidence, when viewed together the majority support a close association among thirst and pOsm and AVP levels.

The positive linear relationship between thirst ratings and pOsm was clearly evident in clinical trials using the hypertonic saline thirst induction method. All the clinical thirst trials that demonstrated this close linear association between thirst scores and their pOsm and AVP correlates also reported conditions and factors that could modify and challenge this osmolality-related thirst or "osmotic thirst" pattern. Variations in osmotic thirst pattern were more apparent in the trials using the water deprivation and/or dehydration-exercise methods. In their study using exercise and controlled hydration, Merry et al. (2008) reported higher pOsm levels among the group of untrained subjects, yet the group of trained subjects had higher thirst scores. O'Neill and colleagues (1997) found only weak correlations between pOsm levels and the thirst ratings of elderly dehydrated nursing-home residents. The attenuated thirst reported by McKenna et al.'s (1999) HONK patients appeared to be disassociated from their high pOsm levels. Cold temperatures attenuated thirst ratings among Kenefick et al.'s (2004) volunteers despite their high pOsm levels. Finally, older

subjects reported lower thirst scores than younger subjects in three age-related thirst trials (P. A. Phillips et al., 1993; Stachenfeld et al., 1997; Takamata et al., 1999).

Under normal circumstances, miniscule upward shifts in pOsm levels cause an immediate compensatory physiologic release of AVP, which acts on the kidneys to conserve water. Investigators observed a positive correlation between AVP and pOsm levels in the majority of the hypertonic saline trials and three of the non-osmotic trials (Argent et al., 1991; Burrell et al., 1992; Figaro & Mack, 1997; Maresh et al., 2004; Martinez-Vea et al., 1993; Merry et al., 2008; E. M. Phillips et al., 1994; Thompson et al., 1991; Wazna-Wesly et al., 1995) along with evidence of similar thresholds for thirst and AVP release. However, similar to osmotic thirst, the correlation between AVP and osmotic increase was modified by older age and environmental conditions.

AVP levels were lower among older compared to younger subjects in two of the osmotic trials (Davies et al., 1995; Farrell et al., 2008). Researchers found significant interactions between time and group for AVP measures only among the younger subjects in a neuroimaging study (Farrell et al., 2008). In Kenefick et al.'s (2004) trial, environmental exposure to cold diminished AVP's fluid regulatory effect despite high pOsm levels in both volunteer groups. In contrast, AVP levels were depressed in the older subjects in heat acclimation trials (Takamata et al., 1999) and delayed in the head-out-of-water immersion study (Stachenfeld et al., 1997). In P. A. Phillips et al.'s (1993) and McKenna et al's (1999) studies, AVP levels were elevated in younger and older subjects as well as in the HONK patient group, respectively, but the older subjects and HONK patients had lower thirst scores than the other groups. The association between thirst and elevated AVP levels is further complicated by the low thirst scores reported by older subjects with depressed AVP levels in two studies (Davies et al., 1995; Takamata et al., 1999). Additionally, fluid-deprived elderly nursing-home residents (O'Neill et al., 1997) and older subjects in the neuroimaging study (Farrell et al., 2008) did not exhibit the normal pattern of rising AVP when challenged with hypertonic saline..

Thirst and pOsm in the Older Adult

The trial outcomes support the close association between thirst and its physiologic correlates but also highlight a number of significant caveats to this association. All the clinical thirst trials demonstrated that this positive association between symptom and physiologic correlates was subject to modification by endogenous and exogenous conditions. The most consistently reported and studied of these modifying factors was older age. Investigators studied advanced age as a modifying factor in six of the reviewed trials and reported that older subjects had lower thirst scores than younger subjects despite elevated pOsm levels and evidence of intact osmotic thirst drive. In addition, McKenna et al. (1999) suggested that "premature aging" of the osmoreceptors in diabetic patients may cause them to be less sensitive to volume deficits thus increasing their risk for severe dehydration.

Authors hypothesized that alterations in AVP's fluid regulation among older adults were due to the reduced renal clearance of AVP. O'Neill et al. (1997) speculated that the absence of change in the AVP levels among dehydrated elderly nursing-home residents was due to a decline in their AVP osmoreceptor function. P. A. Phillips et al. (1993) hypothesized that

aging differentially affects the osmoreceptors of older adults, thus altering baroreceptor sensitivity to volume deficits. This alteration results in reduced thirst, AVP inhibition and potentially result in inadequate fluid replacement. Davies et al. (1995) challenged these explanations, arguing that attenuated thirst reflected the existence of comorbid conditions, such as reduced renal clearance (< 60 ml/min), in older subjects and not their advanced age. These researchers found no significant differences based on age in the relationship between thirst and pOsm in older subjects without the excluded comorbid conditions.

However, Farrell et al. (2008) partially validated these speculations regarding older age as a conditional thirst mediator in their neuroimaging study of osmotic thirst activation and its satiation, or fluid satiety. Positron emission tomography scan images offered evidence that aging may alter the central processing of thirst, thus effecting satiation in older dehydrated adults. Neural brain images revealed age-related alterations in cerebral blood flow to regions in the cingulate cortex that are directly involved in thirst satiation. These alterations in the satiation function could contribute to the attenuated thirst and inadequate fluid intake that distinguish the drinking behavior of older dehydrated adults from their younger counterparts. These findings have important clinical implications for dehydrated older adults, whose age-affected thirst mechanisms may prevent sufficient fluid replacement.

Conclusion

The experimental studies we reviewed here demonstrate that the older adult remains at risk for dehydration and provide some possible physiologic explanations for this risk. The osmotic and nonosmotic pathophysiological factors that may alter the role of thirst in the intricate regulation of fluid homeostasis will continue to challenge clinicians. However, the process of quenching a patient's thirst may serve as the first step in understanding the physiologic forces that control this internal homeostatic world.

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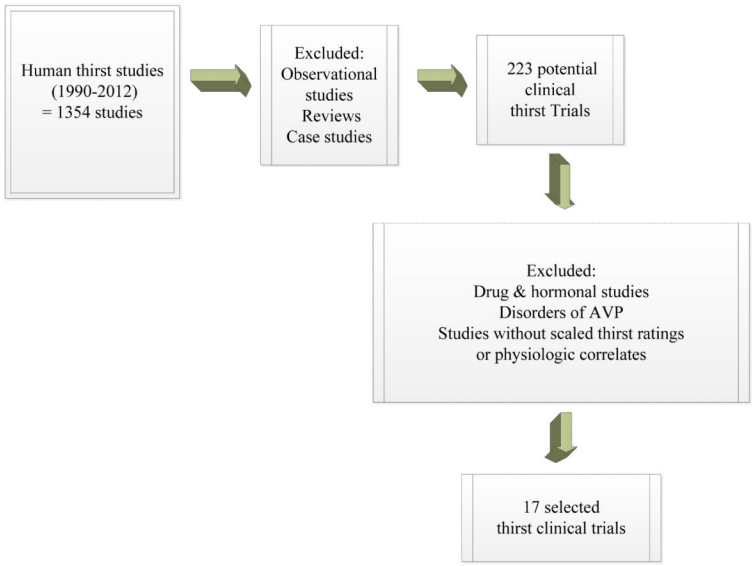

Figure 1.
Literature Search for Clinical Thirst Trials in Human Subjects.

Table 1

Design and Key Findings of Reviewed Thirst Trials.

Author(s) (Year)	Purpose	Sample (Mean Age)	Protocol	Thirst Measures	Results (*r*, if reported, and *p*-values)	Design Score[a]
Argent et al. (1991)	To explore thirst and AVP release in persons with severe chronic kidney disease.	CKD *n* = 8 (*M* 41.4 years); Control *n* = 7 (*M* 41.1 years)	HS at 0.06 ml/min/kg for 2 hr; CKD subjects dialyzed after HS test.	VAS: 0–125 mm uncalibrated line	Thirst increased in both groups, $p < .001$; CKD pre 15 mm ± 4, post 80 mm ± 10; Control pre 23 mm ± 3, post 88 mm ± 11; NS difference between groups. pOsm increased in both groups, $p < .001$; CKD pre 286.3 ± 0.9 mosmol/kg, post 305.5 ± 1.4 mosmol/kg; Control pre 284.9 ± 0.7 mosmol/kg, post 302.1 ± 1.5 mosmol/kg. CKD pre & post AVP levels were significantly higher than controls; authors attributed the difference to reduced clearance in failing kidneys.	6
Thompson et al. (1991)	To test HS and hypoglycemia as stimuli for AVP secretion.	*n* = 8 (*M* 34.1 years)	Insulin bolus 0.1 u/kg and HS at 0.06 ml/min/kg for 2 hr. Study test repeated in < 6 months.	VAS: 0–10 cm uncalibrated line	Thirst ratings increased 1.2 cm ± 0.4 to 7.3 cm ± 0.7 ($p < .001$). pOsm & thirst, $p < .001$; intercepts: $r = 0.84$, slopes: $r = 0.79$ ($p < .001$). AVP & pOsm intercepts: $r = 0.81$, slopes: $r = 0.96$ ($p < .001$).	4
Burrell et al. (1992)	To evaluate the effect of ANH on thirst and AVP in hyperosmolar subjects.	*n* = 6 (*M* 27 years). Subjects blinded to ANH & placebo infusions.	HS at 0.06 ml/min/kg for 1 hr then either ANH at 2 pmol/min/kg for 105 min or placebo at 150 mmol/l (.9%) saline at 0.5 ml/min for 105 min. Treatments given in random order at least 1 month apart.	VAS: 0–10 cm uncalibrated line	ANH plus HS decreased thirst: 1.8 ± 1.1 cm vs. HS & placebo 4.3 ± 0.9 cm ($p < .05$). HS & placebo increased pOsm 286.5 ± 0.8 mosmol/kg to 295.5 ± 1.2 mosmol/kg ($p < .001$); ANH &HS increased pOsm 285.6 ± 1.4 mosmol/kg to 295.8 ± 1.2 mosmol/kg ($p < 0.001$). AVP rose with both ANH & placebo infusions ($p < .01$). ANH had NS effect on pOsm and AVP compared to placebo infusion.	4
Martinez-Vea et al. (1992)	To examine thirst regulation and IDWG in CKD patients.	CKD #1 (IDWG = 5%) *n* = 4 (*M* 58.7 years); CKD #2 (IDWG < 3%) *n* = 5 (*M* 55 years); Controls #3 *n* = 6 (*M* 43.1 years)	HS at 0.05 ml/min/kg for 2 hr. After HS infusion & rehydration CKD patients were dialyzed.	VAS: 0–100 mm line; extreme answers as anchors	CKD#1 had highest thirst ratings vs. CKD #2 & controls #3 ($p < .01$; raw scores graphed, but not reported). CKD #1had lowest pOsm thirst threshold: intercept 277.6 ± 7.6 mosm/kg, slope 0.36 ± .06, $r = 0.96$. AVP increased in CKD #1 3.9 ± .6 to 7.8 ± 2 pg/ml, in CKD#2 4.2 ± .3 to 7.3 ± 1.2 pg/ml; difference between CKD groups NS. No correlation between CKD patients' A-II levels & IDWG.	6
P. A. Phillips et al. (1993)	To examine the effects of drinking on thirst and AVP activity in dehydrated elderly men.	Young *n* = 10 (age 20–32 years); Old *n* = 10 (age 64–76 year.)	No water for 24 hr with dry diet then water loaded at 10 ml/kg with room temperature tap water for < 5 min.	VAS:[b] 0–100 mm line; extreme answers as anchors	Thirst lower in old 2.4 ± 0.8 cm vs. young 4.4 ± 0.5 cm ($p < .05$). pOsm higher in old 294.2 ± 2.8 vs. young 287.7 ± 1.6 ($p < .001$). NS difference in AVP in old vs. young. ANH higher in old 20.3 ± 3.2 pg/ml vs. young 6.5 ± 1.9 pg/ml ($p < .05$). Older subjects' hypodipsia suggests less baroreceptor sensitivity to volume loss.	6

Author(s) (Year)	Purpose	Sample (Mean Age)	Protocol	Thirst Measures	Results (*r*, if reported, and *p*-values)	Design Score[a]
E. M. Phillips et al. (1994)	To compare 20% mannitol with 5% saline as osmotic thirst stimulants.	*n* = 8 (*M* 41.5 years)	HS at 0.06 ml/min/kg vs. 20% mannitol at 0.07 ml/min/kg for 2 hr. HS & 20% mannitol infused in random order.	VAS: 0–10 cm uncalibrated line	Thirst with HS increased 5.1 cm vs 2.6 cm with 20% mannitol ($p < .001$). pOsm higher with HS ($p = 0.04$) vs. 20% mannitol ($p < .0.5$). AVP higher with HS vs. 20% mannitol ($p < .001$). Lower thirst threshold with reduced thirst and fluid intake with rehydration with 20% mannitol.	3
Davies et al. (1995)	To examine effect of aging on thirst, pOsm and AVP response to water and sodium loading.	Young *n* = 10 (*M* 26.8 years); Old (prescreened for disease) *n* = 10 (*M* 72.1 years)	Water loading at 20 ml/kg over 40 min vs 2.7% (462 mmol/l) saline at 0.1 ml/min/kg for 2 hr. Treatments administered randomly with at least 1 week between.	VAS: 0–100 mm line; extreme answers as anchors	NS difference based on age in thirst and pOsm; intercept F (1,214) = 0.02 ($p = 0.8$); slope F (1, 18) = 0.06 ($p < 0.9$). AVP initially lower then rose in older subjects ($p < .001$) with osmotic stimulation. No age-related decline in thirst noted.	9
Wazna-Wesly et al. (1995)	To examine effect of ANH on thirst and AVP response to osmotic stimulus.	*n* = 11 (median 22 years). Randomly assigned to 4 treatments, separated by 7-day intervals.	ANH 2x, 8x & 25x higher dose, or placebo (no ANH) for 2 hr. then HS at 0.1 ml/min/kg for 1 hr.	VAS: 0–10 cm uncalibrated line	Thirst increased with HS infusion ($p < .01$), only; no increase in thirst with three ANH infusions. Thirst & pOsm & no ANH $r = 0.69$ ($p < .01$); thirst & pOsm & 25x ANH $r = 0.83$ ($p < .001$). pOsm & AVP & no ANH $r = 0.86$ ($p < .01$); pOsm & AVP & 25x ANH $r = 0.85$ ($p < .001$). Findings suggest that even high levels of ANH may have only a minor physiologic effect on AVP and thirst regulation.	7
Figaro & Mack (1997)	To examine oropharyngeal receptors' role in fluid replacement in dehydrated humans.	*n* = 6 (age 20–22 years). Randomly assigned to nasogastric water infusion & extraction tests.	Dehydration: exercised 2 hr. at 38°C to induce 2–3% loss in body weight	VAS: 17.5 cm line with anchors at 0 & 12.5 cm	Thirst increased from 1.5 ± 0.6 cm to 9.2 ± 1.0 cm. pOsm increased during dehydration from 282 ± 2 to 289.± 1 ($p < .05$). Thirst & pOsm $r = 0.81$ ($p < .05$). AVP increased from 1.3 ±.2 to 4.4 ± .4 (NS). Oropharyngeal receptors may inhibit AVP release and prevent excessive fluid intake during rehydration.	4
O'Neill et al. (1997)	To examine the response of elderly patients to dehydration.	*n* = 12. Randomly assigned to 1 of 2 groups based on how fluid intake was recorded: *n* = 6 (*M* 82.5 years), *n* = 6 (*M* 80.2 years)	Hydrated 4ml/kg then no water for 16 hr. Dehydration test repeated on 2 separate days in 15-day period.	VAS: 0–10 cm uncalibrated line	Thirst ratings increased with dehydration F (9, 99) = 18.7, $p < .001$. (raw scores graphed, but not reported). pOsm & thirst: $r = 0.28$ ($p < .001$). AVP & pOsm: $r = 0.33$ ($p < .001$). NS change in AVP level during dehydration and rehydration, F (9, 99) = .59 ($p = 0.8$). Average fluid intake 1100 ml per day	6
Stachenfeld et al. (1997)	To examine the effect of tap water immersion on age-related thirst.	Young *n* = 6 (*M* 24 years); Old *n* = 5 (*M* 70 years). All tests performed	Exercised 150 min; water immersion or perfusion suit for 195 min.	VAS: 0–180 mm line; extreme answers as anchors	Thirst ratings higher in young, 94 ± 6 mm, vs. old, 69 ± 8 mm ($p < .05$). pOsm increased in both age groups ($p < .05$). AVP fell with water immersion, delayed decrease in older group. Older subjects' 3-fold higher endogenous ANH level induced by water-immersion	6

Author(s) (Year)	Purpose	Sample (Mean Age)	Protocol	Thirst Measures	Results (*r*, if reported, and *p*-values)	Design Score[a]
		on subjects on separate days at least 2 weeks apart.			test had no effect on thirst, which suggests a reduced sensitivity to volume changes.	
McKenna et al. (1999)	To investigate thirst and AVP response of diabetic survivors of HONK.	HONK *n* = 8 (*M* 70.6 years); Diabetic *n* = 8 (*M* 70.5 years) ; Controls *n* = 8 (*M* 69.8 years)	No water for 8 hr after all subjects achieved stable blood glucose levels.	VAS: 0–10 cm uncalibrated line	Thirst ratings showed lowest rise in HONK group, 0.8 ± 0.3 to 3.5 ± 0.8 cm (p <.001), vs diabetic, 1.0 ± 0.9 to 7.7 ± 1.6 cm, and control, 1.1 ± 0.5 to 7.4 ± 1.3 cm. pOsm measure showed HONK group had highest osmotic threshold, 301.7 ± 2.7 mmol/kg (p < .01), vs diabetic, 294.3 ± 3.2 mmol/kg, and control, 296.9 ± 3.0 mmol/kg. AVP had highest rise in HONK group, 0.9 ± 0.5 to 5.8 ± 1.3 pmol/l (p < .001). Hypodipsia and exaggerated AVP release may predispose HONK patients to severe dehydration	5
Takamata et al. (1999)	To study the effect of exercise-heat acclimation on fluid regulation in dehydrated older men.	Young *n* = 6 (*M* 24.7 years); Old *n* = 9 (*M* 70 years)	Acclimation: 4 exercise-heat rounds with 2 hr rehydration for 6 consecutive days.	VAS:[b] 0–18 cm; intersecting line 0 cm = not thirsty at all & 12 cm = extremely thirsty	Thirst ratings higher pre-acclimation in young, 56.0 ± 3.2 mm, vs old, 26.1 ± 9.4 mm (p <.05). Thirst ratings correlated, r = 0.69, with fluid intake in young group. pOsm similar between age groups; baseline pOsm higher in old group. AVP increase less in old vs. young pre- and post-acclimation tests. Acclimation did not improve fluid regulatory function in the older subjects. Lower PRA suggests diminished osmosensitivity to hypovolemia.	6
Kenefick et al. (2004)	To examine thirst and AVP response at rest and during exercise-cold exposure.	*n* = 8 (*M* 35.1 years); *n* = 9 (*M* 21.3 years). Groups were recruited from different subject pools. Each subject assigned to 4 exercise-test sessions in random order.	Walking or standing for 60 min euhydrated or hypohydrated in 4°C or 27°C conditions.	NRS: 9-point scale; anchors, 1 = not thirsty, to 9 = very, very thirsty	Thirst 40% lower in euhydrated and hypohydrated cold tests. pOsm higher in hypohydrated vs euhydrated tests (p < .05). AVP declined (66%) post exercise & cold: 5.9 ± 0.5 to 2.0 ± 0.3 pgml (p < .05). Decrease in AVP with cold exposure despite positive correlation between pOsm and AVP (r = 090) in hypohydrated tests.	6
Maresh et al. (2004)	To examine the effect of hydration on thirst and correlates during low-intensity exercise in the heat.	*n* = 10 (*M* 21 years). Each subject randomly assigned to 4 hydration & water-intake tests.	4 days of exercise in 33°C for 3–4% weight loss then either eu- or hypohydrated.	NRS: 9-point scale; anchors, 1 = not thirsty, to 9 = very, very thirsty	Thirst highest in hypohydration + no water, 5.47 ± .76 (p < .05), vs euhydration + water, 1.59 ± .41. pOsm highest in hypohydration + no water, 296 ± 3 mosmol/kg, vs euhydration + water, 287 ± 2 mosmol/kg. AVP highest in hypohydration + no water despite no change in pOsm (p < .05). Findings suggest that pOsm and AVP have greater effect on thirst and drinking than the RAAS.	4
Farrell et al. (2008)	To use positron emission tomography (PET) to measure effect of older age on cerebral blood	Young *n* = 10 (*M* 23.7 years); Old *n* = 12 (*M* 68.1 years)	HS at 3.1 ml/kg for ~ 68.5 min. HS infusion during PET scan.	VAS: 0–10 cm uncalibrated line	Thirst rose with HS over time F (3, 60) = 28.1 (p < .001); NS difference in thirst between age groups. pOsm rose with HS in both age groups F (4, 80) = 24.3 (p < .001); NS difference between age groups; no significant interaction between group and time. AVP interaction between time and group F (4,72) = 2.9 (p <	6

Author(s) (Year)	Purpose	Sample (Mean Age)	Protocol	Thirst Measures	Results (*r*, if reported, and *p*-values)	Design Score[a]
	flow with osmotic thirst.				.05) only in young; NS difference in AVP measures in old group. PET scans indicate that reduced intake in older subjects may be due to changes in central (brain) processing involving the satiation of thirst.	
Merry et al. (2008)	To explore effect of physical fitness on alterations in fluid regulation in response to hypohydration.	Trained $n = 6$ (M 30.6 years); Untrained $n = 6$ (M 25.2 years). Randomized crossover assignment to pre-hydration and post-rehydration tests.	Consumed either 500 ml or 20 ml fluid bolus; exercised for 80 min then rehydrated to replace 20% or 100% body mass lost.	NRS: 9-point scale	Thirst higher in trained, 4.0 ± 1.5, vs. untrained, 2.7 ± 1.2 ($p < .05$). pOsm and thirst $r^2 = 0.93$ during fluid-intake phase. AVP slope greater in untrained, 0.47 ± .06 mosmol, vs. trained, 0.25 ± .05 mosmol ($p < .05$). AVP show effects of fitness ($p = .02$) & interaction of fitness with hydration ($p = .05$). Trained had 34% ($p < .01$) higher sweat rate than untrained. Aerobic fitness may alter neurohormonal fluid regulatory response to dehydration.	6

Note. A-II = plasma angiotensin II (pg/ml); ANH = atrial naturetic hormone (pg/ml); AVP = arginine vasopressin peptide (pg/ml); CKD = chronic kidney disease; HONK = hyperosmolar non-ketotic coma; HS = hypertonic (5%) saline (855 mmol/l NaCl); IDWG = interdialytic weight gain; NRS = numeric rating scale; NS = nonsignificant; pOsm = plasma osmolality (mosm/kg); PRA = plasma renin activity (precursor hormone for A-II); RAAS = renin angiotensin aldosterone system; VAS = visual analogue scale.

[a]Evaluation of study design quality was based on the following criteria: description of appropriate randomization procedures, description of blinding procedures, information provided about withdrawals and dropouts, the inclusion of one or more control or comparison groups, a clear description of the intervention protocol, and use of validated intervention measures. Each study was given a score of 0–2 for each criterion (0 = absent, 1 = partially described, 2 = clearly described), with the highest possible quality score for a study being 12. Scores ≤ 5 indicate low-quality design; scores ≥ 6 indicate high-quality design. All reviewed studies were limited by small sample sizes.

[b]VAS thirst score reported in cm or mm.