# CENTRAL DIABETES INSIPIDUS

CHI Formulary Indication Review

مجلس الضمان الصحي
Council of Health Insurance

**INDICATION UPDATE**

**ADDENDUM- November 2023**

**To the CHI Original Central Diabetes Insipidus Clinical Guidance- Issued May 2020**

# Table of Contents

## Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

## List of Tables



## List of Figures

# Abbreviations

| | |
|---|---|
| ADH | Anti-Diuretic Hormone |
| ADI | Adipsic Diabetes Insipidus |
| AVP | Arginine Vasopressin |
| CADTH | Canada's drug and health technology agency |
| CDI | Central Diabetes Insipidus |
| CHI | Council of Health Insurance |
| CPG | Clinical Practice Guideline |
| dDAVP | deamino D-Arginine Vasopressin, Desmopressin |
| DI | Diabetes Insipidus |
| EMA | European Medicines Agency |
| FDA | Food and Drug Administration |
| HAS | Haute Autorité de Santé |
| HTA | Healthy Technology Assessment |
| ICU | Intensive Care Unit |
| IDF | CHI Drug Formulary |
| IQWIG | Institute for Quality and Efficiency in Health Care |
| MRI | Magnetic resonance imaging |
| NDI | Nephrogenic Diabetes Insipidus |
| NICE | National Institute for Health and Care Excellence |
| PBAC | Pharmaceutical Benefits Advisory Committee |
| SFDA | Saudi Food and Drug Authority |
| SIAD | Syndrome of Inappropriate Anti-Diuresis |
| TBI | Traumatic Brain Injury |
| WDT | Water deprivation test |

# Executive Summary

In 2022, a working group comprising members from both national and international endocrinology and pediatric endocrine societies including the Endocrine Society, the European Society of Endocrinology, the Pituitary Society, the Society for Endocrinology, the European Society for Pediatric Endocrinology, the Endocrine Society of Australia, the Brazilian Endocrine Society, and the Japanese Endocrine Society suggested the name “diabetes insipidus” be changed to “arginine vasopressin deficiency (AVP-D)" for cases with central causes and "arginine vasopressin resistance (AVP-R)" for cases with nephrogenic causes. This change was endorsed by all the aforementioned societies who were represented by the working group members and is currently under review at several other societies[1].

The three main reasons for the name change include[1]:

1. While the terms mellitus and insipidus effectively distinguish between the clinical features of these two distinct polyuria causes and are not eponyms, the shared use of the term "diabetes" in both has regrettably created confusion for both patients and their caregivers.
2. Additionally, individuals with diabetes insipidus are strongly advocating for a name change that excludes the term "diabetes," primarily due to their encounters with healthcare providers who lacked a clear understanding of the condition and often confused it with diabetes mellitus.
3. Ultimately, it is believed that medical condition names should ideally mirror the underlying pathophysiology, and in the instance of diabetes insipidus, it is now well-established that the condition arises from the inadequate secretion and/or the impact on end organs of the hormone arginine vasopressin (AVP).

However, throughout the report, we will still refer to it as central diabetes insipidus or CDI since the name change has not been widely adopted by the guidelines and review articled discussed.

Diabetes insipidus (DI) is characterized by the excretion of substantial amounts of diluted urine (more than 3 liters per day) with a low concentration (less than 300 milliosmoles per kilogram). DI is categorized into two primary forms: central and nephrogenic. Central DI is identified by a reduced secretion of antidiuretic hormone (ADH), also known as arginine vasopressin (AVP). This deficiency results in increased urination and thirst because it impairs the individual's capacity to concentrate urine. Central diabetes insipidus (DI) can be attributed to a variety of factors including idiopathic, malignant, or benign tumors of the brain or pituitary, cranial surgery, and head trauma[2].

Central diabetes insipidus (CDI) is a rare condition in the United States, affecting approximately 3 individuals per 100,000 in the population. There are no notable

variations in the prevalence of central or nephrogenic DI based on gender, with an equal occurrence in both males and females. Likewise, there are no significant variations in prevalence observed among different ethnic groups[2]. In Saudi Arabia, the estimated incidence is 3,869 in 25,795,938 population, i.e., 1.5 in 10,000 people[3].

Excessive urination, increased thirst, and nighttime urination are the primary symptoms of diabetes insipidus (DI). While the daily amount of urine remains fairly consistent for each individual, it can vary significantly from one patient to another, ranging between 3 and 20 liters. When a patient shows signs indicating the possibility of having diabetes insipidus (DI), it is essential to conduct diagnostic laboratory examinations to confirm the condition. This includes a 24-hour collection of urine to assess urine volume. Additionally, healthcare providers should measure the following parameters: serum electrolytes and glucose, urinary specific gravity, simultaneous plasma and urinary osmolality, and plasma antidiuretic hormone (ADH) level. Other tests include water deprivation testing and head MRI[2].

Fluid replacement therapy and desmopressin are the treatment of choice in CDI. Other pharmacological options for treating DI include synthetic vasopressin and non-hormonal medications such as chlorpropamide, thiazides, carbamazepine, and clofibrate. It is worth noting that clofibrate, which was previously available in the United States, is no longer on the market. Carbamazepine is rarely prescribed due to its associated side effects and is typically considered only when all other treatment approaches have proven ineffective[2].

**CHI issued Central diabetes insipidus clinical guidance after thorough review of renowned international and national clinical guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.**

**This report functions as an addendum to the prior CHI Central diabetes insipidus clinical guidance** and seeks to offer guidance for the effective management of **Central diabetes insipidus**. It provides an **update on the** Central diabetes insipidus **Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

**The main trigger for this update is the issuance of updated versions of previously reviewed guidelines** namely: Recommendations discussed in a review article published **in the journal of clinical endocrinology in 2022** on Diagnosis and management of central diabetes insipidus in adults. Moreover, **new guidelines** are added to the report such as a review article in the cureus journal of medical science on Diabetes Insipidus: Pathogenesis, Diagnosis, and Clinical Management (**2021**) and the **Sydney's Children's Hospital Network** practice guideline for the inpatient management of central diabetes insipidus (**2023**).

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is recommended that **hydrochlorothiazide** be added to the CHI drug formulary. Furthermore, PA and MD (prescribing edits) for Dextrose, Sodium Chloride solutions should be removed since there is no need for them.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Central diabetes insipidus management.

Below is a table summarizing the major changes based on the different central diabetes insipidus guidelines used to issue this report:

**Table 1.** General Recommendation for the Management of Central Diabetes Insipidus

| Management of Central Diabetes Insipidus | | |
|---|---|---|
| **General Recommendations** | **Level of Evidence/Grade of Recommendation** | **Reference** |
| **The water deprivation test (WDT) is the most frequently employed diagnostic examination.** | Not graded | Tomkins et al. (2022)[4] |
| The primary aspect of symptom control involves ensuring that fluid intake surpasses fluid loss, with a strong focus on preserving the individual's quality of life. | Not graded | Mutter et al. (2021)[5] |
| The typical approach to treating CDI and gestational DI involves administering synthetic antidiuretic hormone (ADH), known as desmopressin (DDAVP) | Not graded | Mutter et al. (2021)[5] |
| DDAVP can be administered through oral, intranasal, or parenteral routes. | Not graded | Mutter et al. (2021)[5] |
| **In instances of central diabetes insipidus (DI) in infants whose nutrition depends on fluid intake, an endocrinologist might choose a treatment strategy that combines a low-solute diet, such as breast milk, with a thiazide diuretic as an alternative to using desmopressin.** | Not graded | The Sydney Children's Hospital Network 2023[6] |

# Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Central diabetes insipidus report, and the second includes **newly added guidelines** that have helped in generating this report.

## 1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the May 2020 CHI Central diabetes insipidus and the corresponding recommendations:

**Table 2.** Guidelines Requiring Revision

| **Guidelines Requiring Revision** | |
|---|---|
| **Old Versions** | **Updated versions** |
| 1.1 **Society for Endocrinology Clinical Guidance** for Inpatient management of cranial diabetes insipidus **2018** | N/A* |
| 1.2 Recommendations discussed in a review article published in **the journal of clinical endocrinology in 2018** on Diagnosis and management of central diabetes insipidus in adults | N/A* |
| 1.3 **Clinical guidelines for management of diabetes insipidus** and syndrome of inappropriate antidiuretic hormone secretion after pituitary surgery **2014** | N/A* |
| 1.4 Review article published in **Obstetrician & Gynecologist journal in 2017** about Diabetes insipidus in pregnancy | N/A* |
| 1.5 Mini review about Diabetes insipidus--diagnosis and management. **Hormone Research in Pediatrics published 2012** | N/A* |

*****: *No updated versions available*

## 1.2 Additional Guidelines

This part includes the added guidelines and review articles to the previous CHI Central Diabetes Insipidus report, along with their recommendations.

**Table 3.** List of Additional References

| Additional Guidelines |
| --- |
| Diagnosis and Management of Central Diabetes Insipidus in Adults: Review Article Published in the Journal of Clinical Endocrinology & Metabolism (Tomkins et al., **2022**) |
| Diabetes Insipidus: Pathogenesis, Diagnosis, and Clinical Management: Review Article Published in Cureus (Mutter et al., **2021**) |
| The Sydney Children's Hospital Network Practice Guideline for Inpatient Management of Central Diabetes Insipidus (**2023**) |

### 1.2.1 Diagnosis and Management of Central Diabetes Insipidus in Adults: Review Article Published in the Journal of Clinical Endocrinology & Metabolism (2022)

This 2022 review focuses on the diagnosis and management of CDI, providing insights into the physiological disturbances underpinning the syndrome and particular emphasis on management of fluid intake and pharmacological replacement of arginine vasopressin (AVP). Specific clinical syndromes such as adipsic DI and DI in pregnancy as well as management of the perioperative patient with DI are discussed[4].

**Diagnosis of CDI**

- Establishing the presence of hypotonic polyuria is the essential first step, as 15% of referral cases have normal urine volume; urinary frequency, secondary to infection, prostatism, or irritable bladder, is often misdiagnosed as polyuria.
- Once polyuria is confirmed, confounding conditions such as diabetes mellitus, renal impairment, hyperglycemia, hypercalcemia, and hypokalemia should be excluded by baseline laboratory tests.
- The water deprivation test (WDT) is the most used test. This is a 2-step test: an initial 8-hour period of water deprivation followed by administration of parenteral desmopressin.

**Clinical priorities for management of DI**

- Abolition of symptoms of polyuria and polydipsia
- Avoidance of hyponatremia secondary to treatment
- Treatment of underlying disorders and associated hormonal abnormalities
- Monitoring of quality of life
- Communication of sick day rules to cover vomiting illness etc.
- Liaison with other medical professionals, particularly surgeons and anesthetists to ensure safe negotiation of surgery

**Management of Fluid Intake**

- Hypothalamic control of thirst remains intact in the majority of CDI patients, allowing them to naturally adjust fluid intake to compensate for renal water losses.
- Therefore, hypernatremia, which serves as the primary indicator of insufficient fluid intake, is a rare occurrence in CDI patients who have unrestricted access to fluids.
- Some CDI patients, constituting a minority, may experience damage to their osmoreceptors, leading to hypodipsia and adipsic diabetes insipidus (ADI). These patients need to be trained to adhere to fixed fluid intake regimens to prevent the risk of hypernatremic dehydration.
- Certain clinical conditions, such as vomiting or diarrheal illnesses, not only limit the ability to consume oral fluids but also impede the retention of oral desmopressin. Consequently, these conditions can rapidly escalate to hypernatremic dehydration, underscoring the importance of patients seeking prompt medical advice during episodes of gastroenteritis or prolonged vomiting.
- The development of "sick day rules," like those typically provided to individuals undergoing glucocorticoid therapy, can prove beneficial in this context.
- Evidence suggests that the management of fluid balance in hospitalized patients with diabetes insipidus during acute illness may be less than optimal, resulting in frequent occurrences of both hypernatremia and hyponatremia.

**Pharmacological Management of CDI**

- Arginine vasopressin (AVP), a nonapeptide hormone, has a brief plasma half-life, lasting only 5 to 10 minutes.

- Its primary physiological action involves the transient induction of aquaporin 2 water channel synthesis postreceptor and the insertion of pre-existing aquaporin 2 water channels into the apical cell membrane of the distal collecting duct.
- Due to its short duration of action, AVP is not suitable for therapeutic use in managing CDI.
- A synthetic analog called desmopressin (dDAVP) has been developed, extending its half-life from 5 minutes to 6 to 8 hours by removing the amino group of the cysteine amino acid.
- dDAVP can be administered two or three times daily, making it a viable therapeutic option.
- Additionally, dDAVP replaces D-arginine for L-arginine, eliminating the vasopressor effects of AVP.
- dDAVP maintains an antidiuretic/vasopressor ratio of approximately 3000, ensuring it lacks vasoconstrictor effects, which could pose risks in patients with arterial disease.
- dDAVP is available in parenteral, oral, and nasal forms for various administration routes.

**Oral dDAVP**

- Most patients prefer oral desmopressin (dDAVP) over nasal spray because of its ease of administration and continued effectiveness even during nasal congestion caused by infections.
- Peak clinical action is observed within 2 hours of oral ingestion, and the antidiuretic effect can last for 6 to 12 hours.
- There is significant variability in dDAVP absorption among patients, but in clinical practice, food intake does not appear to be a significant concern.
- The duration and magnitude of antidiuretic action are directly related to the dDAVP dose.
- Available oral preparations include standard tablets and sublingual "desmotabs melt," both commonly used.
- dDAVP is generally well-tolerated with few major side effects, although hyponatremia is a notable potential side effect.

**Nasal dDAVP**

- The earliest treatment for chronic CDI was the intranasal formulation of desmopressin (dDAVP).
- It can be administered either as a metered dose spray or through a rhinyl tube and achieves a quicker time to reach peak drug concentration compared to oral dDAVP. However, the time to reach peak antidiuretic activity is similar.
- The duration of the antidiuretic effect varies more with the nasal formulation, ranging from 5 to 21 hours.
- Nasal dDAVP's effectiveness is affected by conditions like nasal mucosa inflammation, congestion, or scarring. It is also contraindicated after transsphenoidal surgery when nasal packing may be used.
- Patients with visual impairments may find the administration process challenging.

**Parenteral dDAVP**

- Desmopressin (dDAVP) can be administered either intravenously or subcutaneously.
- Following an intravenous dose of 1 µg, the peak antidiuretic response is observed within 12 hours. Increasing the dosage to 8 µg extends the duration of action to 48 hours.
- Parenteral dDAVP is beneficial in perioperative situations and for managing transient CDI following traumatic brain injury (TBI) or transsphenoidal surgery.

**Other treatments**

- Carbamazepine directly stimulates V2 receptors, promoting the synthesis of aquaporin 2 expression, which in turn enhances water reabsorption.
- Chlorpropamide augments the action of AVP by increasing the expression of V2 receptors. However, its clinical utility is constrained by the risk of hypoglycemia.
- Clofibrate triggers the release of AVP from the neurohypophysis.
- None of these alternative agents possess similar effects to the mentioned ones.

**Management of acute central DI**

- The occurrence of acute onset CDI is most observed following surgical procedures for pituitary tumors using the transsphenoidal or transcranial approach. It can also occur after traumatic brain injury (TBI) and subarachnoid hemorrhage.
- The treatment approach involves minimizing renal water losses by administering dDAVP at a dosage of 1 to 2 µg through intramuscular or subcutaneous routes. In cases of transient CDI, a single dose may sometimes be adequate for subsequent administration.
- Patients should be encouraged to drink water as per their thirst. In cases of cognitive impairment, appropriate intravenous fluids can be administered to maintain normal sodium levels (eunatremia).
- Acute CDI is often temporary and may resolve after a single parenteral dose of dDAVP. Additional parenteral doses are necessary only if excessive urination persists.
- A recent survey conducted among pituitary endocrinologists indicates a strong consensus for the use of "on-demand" postoperative dDAVP rather than regular dosing.
- Continuous dDAVP treatment is only recommended if polyuria continues beyond 48 hours, as there is an occasional triphasic response.
- It is essential to closely monitor plasma sodium levels and urine volume. If a positive fluid balance and declining plasma sodium concentration occur, it suggests the development of Syndrome of Inappropriate Anti-Diuresis (SIAD). In such cases, dDAVP should be discontinued, and fluid intake should be restricted.
- Stopping dDAVP before hospital discharge helps determine if natural AVP secretion is recovering.
- If dDAVP continues after hospital discharge, patients should be informed about the potential risk of the triphasic response. They should also be advised to monitor for symptoms suggestive of hyponatremia, like headaches and bloating, and undergo plasma sodium measurements if such symptoms arise.
- Post-discharge, patients should undergo retesting to assess the recovery of posterior pituitary function. This reevaluation is typically recommended at 3 to 6 months after leaving the hospital.

**Management of chronic central DI**

- Symptomatic relief is typically rapid upon commencing dDAVP, and it offers effective long-term management of polyuria.
- In cases of incomplete AVP deficiency (partial CDI), a single nighttime dose can effectively control nocturia, ensuring uninterrupted sleep, as long as daytime symptoms are manageable.
- A single nighttime dose also helps with daytime aquaresis, reducing the risk of dilutional hyponatremia.
- Patients with complete AVP deficiency (complete CDI) may require oral dDAVP administration 2 to 3 times daily.
- If hypernatremic dehydration occurs, addressing electrolyte and fluid deficiencies is crucial.
- Mild hypernatremia (plasma sodium 145-148 mmol/L) can often be managed by ensuring free access to drinking water and encouraging oral intake. However, if the patient experiences hypotension or cognitive decline, intravenous administration of isotonic saline is recommended.
- Severe hypernatremia (plasma sodium >149 mmol/L) may necessitate the use of hypotonic fluids, such as nasogastric water or intravenous infusion of 5% dextrose in water.

**Management of CDI during fasting, and perioperative care**

- The Society for Endocrinology guidelines emphasize the need for a collaborative plan involving the surgical, anesthetic, and endocrine teams regarding dDAVP and fluid replacement.
- The endocrine team oversees the administration of parenteral dDAVP during the perioperative period.
- Continuous monitoring of electrolytes and the use of isotonic fluids are maintained during fasting.
- Planning the transition back to oral fluids and dDAVP should also involve input from the endocrine team.

**Use of alcohol in CDI**

- Patients with CDI are advised to exercise caution regarding alcohol consumption.
- Consistent alcohol consumption over time has been linked to chronic hyponatremia.

- Binge drinking, particularly large volumes of beer, can induce acute hyponatremia in both healthy individuals and CDI patients receiving dDAVP therapy.
- Regular use of dDAVP can pose risks when significant alcohol consumption, especially beer, is considered.
- Omitting the evening dose of dDAVP to prevent hyponatremia can result in substantial polyuria due to the combined effects of drug withdrawal and fluid intake.
- Consuming small quantities of wine or spirits is not linked to significant hyponatremia.
- Many young individuals with CDI seek advice on how to manage their medication while consuming alcohol. The primary recommendation is always abstinence, with moderation as an alternative. For social events traditionally involving alcohol, we suggest skipping the evening dose of dDAVP to promote aquaresis. This strategy helps prevent severe acute hyponatremia but may lead to uncomfortable nighttime urination.

**DI in pregnancy**

- Temporary DI associated with pregnancy is typically addressed using dDAVP, and this treatment can generally be discontinued within two months after giving birth.
- dDAVP is not metabolized by cysteine aminopeptidase, making it a suitable treatment for gestational diabetes insipidus. However, some individuals with pre-existing CDI may need higher dDAVP doses.
- dDAVP is categorized as a category B drug by the Food and Drug Administration. There is no animal data to suggest fetotoxicity or teratogenicity, and no data in human pregnancy.
- While the available data are derived from limited sample sizes, there is no substantial evidence indicating that dDAVP poses a greater risk to either the mother or the child compared to the clinical necessity of treating a pregnant mother with CDI.
- As dDAVP is altered to eliminate the vasoconstrictor properties of the original compound, it should not impact maternal blood pressure or increase the risk of pre-eclampsia. Additionally, because dDAVP lacks an affinity for V1 receptors in uterine myometrium, it is not linked to preterm labor.
- The transfer of dDAVP to breast milk is minimal, and it has no effect on the infant's water balance.

**Adipsic DI**

- In a minority of individuals, the injury causing AVP deficiency also harms the osmoreceptors in the anterior hypothalamus, resulting in adipsic diabetes insipidus (ADI).
- The initial instances of ADI were documented in patients who had undergone surgical clipping of aneurysms in the anterior communicating artery (ACOM) following a Subarachnoid Hemorrhage (SAH).
- Treatment for ADI involves a twice-daily administration of dDAVP to regulate urinary output.
- A fixed fluid intake is also established, with the optimal volume typically determined through inpatient observations at the time of diagnosis.
- After establishing a baseline eunatremic weight and stabilizing plasma sodium level, which is often achieved with a daily fluid intake of 1.5 to 2 liters, adjustments in fluid intake can be calculated based on factors such as climate, physical activity, and the presence of concurrent illnesses.
- Patients are instructed to weigh themselves daily. A sudden drop from the eunatremic weight may indicate dehydration, necessitating an increase in hypotonic fluid intake to replace fluid deficits.
- Conversely, abrupt weight gain may indicate fluid overload and an increased risk of hyponatremia.
- Regular check-ups are advised, including frequent measurements of plasma sodium concentration to help interpret weight fluctuations.
- Published case series suggest a potential clinical benefit in using chlorpropamide to stimulate thirst.
- However, the risk of hypoglycemia associated with these agents makes it unlikely that any modest clinical improvement justifies their use.
- Behavioral modification therapy has been proposed as an adjunctive treatment.
- Nonetheless, the primary focus of care still revolves around training patients to consume predetermined daily fluid volumes, which remains the most crucial aspect of management.

### 1.2.2 Diabetes Insipidus: Pathogenesis, Diagnosis, and Clinical Management: Review Article Published in Cureus (2021)

The following recommendations are retrieved from a review article published in the Cureus journal of medical science on **Diabetes Insipidus: Pathogenesis, Diagnosis**, and Clinical Management[5]:

- While diabetes insipidus (DI) is a rare endocrine disorder, leaving it untreated can have adverse effects on the patient's quality of life.
- DI can be categorized into four primary types: central, nephrogenic, dipsogenic, or gestational. In adults, DI is typically characterized by a daily urine output exceeding 3-3.5 liters, accompanied by a urine osmolality of less than 300 mOsmol/kg.
- The primary categories of DI include central (neurogenic) and nephrogenic forms.
- The more prevalent variant, known as central diabetes insipidus (CDI), arises from a deficiency in anti-diuretic hormone (ADH) production.
- This deficiency is primarily attributed to acquired factors such as traumatic brain injuries (TBI), infections, hemorrhage affecting the posterior pituitary or hypothalamus, neurosurgical procedures, and the presence of tumors.
- While the initial causes of these conditions may differ, all types result in the production of copious amounts of diluted urine, intense thirst, and severe dehydration. Human water balance primarily relies on three interconnected factors: thirst, the synthesis and release of ADH, and the normal functioning of the kidneys.

**Table 4.** Summary of Causes, Vasopressin Response, Diagnosis, and Clinical Management of Diabetes Insipidus. Retrieved from Mutter CM, Smith T, Menze O, Zakharia M, Nguyen H. Diabetes Insipidus: Pathogenesis, Diagnosis, and Clinical Management. Cureus. Published online February 24, 2021. doi:10.7759/cureus.13523.

| | Central DI | Nephrogenic DI | Dipsogenic DI | Gestational DI |
|---|---|---|---|---|
| Description | Deficiency in release of ADH/AVP from posterior pituitary | Decreased response to ADH/AVP or mutations in AQP2 | Abnormally low thirst threshold leading to excessive thirst | Excessive placental vasopressinase |
| Causes | Brain injury; Infection; Loss of blood to posterior pituitary/hypothalamus; Neurosurgery; Tumor; Genetic defects in ADH synthesis | Lithium therapy; Foscarnet; Clozapine, congenital defect in AQP2 gene; Hypercalcemia; Hypokalemia; Protein malnutrition; Aging | Excessive fluid intake due to psychotic or neuro-developmental disorders; Damage to the hypothalamus; Hippocampus deformations; Brain lesions to the amygdala; Stress-reducing behaviors Genetics | Pregnancy; Genetics; Diet; Sedentary lifestyle |
| Vasopressin Response | Responds by normalizing urine osmolality | Does not respond/urine osmolality does not change | Does not respond/urine osmolality does not change | Responds by normalizing urine osmolality |
| Diagnosis | Urine osmolality increases >50% following water deprivation and DDAVP administration; Copeptin <4.9 pmol/L following osmotic stimulation MRI of pituitary gland | Urine osmolality increases <50% following water deprivation and DDAVP administration Baseline copeptin >21.4 pmol/L | Excretion of dilute urine exceeding 40-50 ml/kg of body weight | Serum osmolality greater than 285 mOsm/kg with persistent urine osmolality less than 300 mOsm/L. |
| Management | DDAVP; Thiazide diuretics; Fluids | Discontinue contributing therapy/medication, Thiazide diuretics, fluids, renal diet (low sodium, protein, and phosphorous) | Behavioral therapy (reduce water intake and balanced diet); Antipsychotic medications | DDAVP |

**Evaluation and differential diagnosis**

- In clinical practice, assessing a patient includes conducting a comprehensive medical history and physical examination, along with determining plasma osmolality and measuring the total 24-hour urine volume to confirm polyuria. Establishing baseline measurements of urine osmolality, plasma electrolytes, and random serum values is also essential during the diagnostic process.
- Common initial symptoms in patients typically involve excessive thirst (polydipsia), increased urine output (polyuria), and nighttime urination (nocturia).

**Diagnosis**

- The indirect water deprivation test involves:
    1. Depriving the patient of fluids.
    2. Regularly measuring urinary excretion, urine osmolality, plasma sodium, and plasma osmolality.
    3. Continuing fluid deprivation for a maximum of 17 hours or until plasma sodium concentration reaches 150 mmol/L or a body weight loss of 3%-5% occurs.
    4. Administering synthetic ADH (desmopressin or DDAVP).
    5. Comparing urine osmolality before and after DDAVP administration.
- In healthy individuals, at the end of the test:
    - ✓ Urine osmolality should be above 800 mOsm/kg.
    - ✓ There should be no increase in urine osmolality following DDAVP administration.
- Both nephrogenic and central DI will exhibit urine osmolality below 300 mOsm/kg.
- The indirect water deprivation test is not routinely used in pregnancy. If it is used in a pregnant patient, close observation is necessary.
- Copeptin is a recent clinical diagnostic marker for DI, and it is highly correlated with plasma arginine vasopressin (AVP).
- Both copeptin and AVP originate from the same precursor protein called pre-provasopressin.
- Copeptin surpasses AVP as a diagnostic marker because copeptin results can be obtained in under two hours, and it necessitates only a small plasma or serum sample of 50 µL.
- An MRI of the pituitary gland can also be used to diagnose CDI.

**Treatment**

- Managing DI is essential for enhancing the patient's quality of life, and the extent to which symptoms can be alleviated depends on the underlying cause of the disorder.
- First-line treatments are available for both central and nephrogenic DI to help maintain fluid balance.
- Ensuring constant access to water is critical to prevent rapid dehydration.

- A counterintuitive approach used to manage CDI and nephrogenic diabetes insipidus (NDI) involves the use of thiazide diuretics, which inhibit the NaCl cotransporter in the renal distal convoluted tubule.
- The preferred treatment for CDI is desmopressin (DDAVP), which is a synthetic form of ADH (antidiuretic hormone).
- DDAVP has a much weaker antidiuretic effect compared to natural ADH, with a 2,000-3,000-fold lower potency.
- DDAVP can be administered through oral, intranasal, or parenteral routes.
- Intranasal or oral administration is considered the most effective, with plasma concentrations reached in approximately 40-55 minutes.
- Typically, urine output decreases within one to two hours after DDAVP administration, and the effect can last from 6 to 18 hours.
- Rare side effects associated with intranasal DDAVP include eye irritation, headache, dizziness, rhinitis, or epistaxis (nosebleed), coughing, flushing, nausea, vomiting, abdominal pain, chest pain, palpitations, and tachycardia.

**Prognosis and prevention**

- The quality of life after the onset and treatment of DI can vary significantly based on the underlying cause.
- While advancements have improved the identification of DI types and causes, the disorder's diversity, severity, and genetic factors mean that no single treatment can completely relieve symptoms for all patients.
- In instances where CDI is triggered by severe trauma or head injury, it not only reduces the patient's quality of life but can also lead to additional complications for both the patient and their family.

### 1.2.3 The Sydney Children's Hospital Network Practice Guideline for Inpatient Management of Central Diabetes Insipidus (2023)

The recommendations published by this practice guideline should be used for patients > 4 weeks of age admitted to inpatient wards and Emergency Departments and may be used in ICU and operating theatres/recovery as appropriate, alongside ICU policies. It is also intended for use in conjunction with endocrine team consultation[6]. The main recommendations are detailed below.

- Central DI occurs mainly in the following circumstances:
    - Congenital abnormality of pituitary development (congenital hypopituitarism). Presence of a pituitary fossa tumor.

    - Post-operatively after resection of a pituitary fossa tumor or by damage to the pituitary stalk.
    - Head trauma, intracranial hemorrhage or infection, brain death.
- CDI, particularly when triggered by a pituitary fossa tumor or surgical removal, can lead to the loss of the natural sensation of thirst. This makes patients prone to severe dehydration and elevated sodium levels (hypernatremia). Likewise, patients who still have a functioning thirst mechanism but are unable to drink in response to their thirst are also at risk of dehydration and hypernatremia.

**Clinical definition of diabetes insipidus**

- Urine volume > 4 mL/kg/hour for at least 2 hours, AND
- Urine specific gravity ≤ 1.005 or urine osmolality < plasma osmolality, AND
- Serum sodium > 145 mmol/L and plasma osmolality >300 mOsm/kg (if accurate fluid replacement has not occurred)

It is crucial to differentiate between appropriate diuresis following the administration of large IV sodium chloride 0.9% and diabetes insipidus (DI), as they have distinct characteristics. Appropriate diuresis is typically observed after surgery, is associated with good hydration status, and does not necessitate treatment. To distinguish between the two, medical professionals can assess intra-operative fluid input and output, evaluate hydration status based on parameters such as body weight, blood pressure, and heart rate, and consider measuring urinary sodium and osmolality. In DI, urinary sodium is usually low, whereas it is high after excessive IV sodium administration.

**Post-operative diabetes insipidus**

Post-operative diabetes insipidus (DI) can manifest as either transient, permanent, or follow a triphasic pattern:

- Transient DI typically emerges suddenly on the first day after surgery and typically resolves within a few days.
- The triphasic pattern consists of three phases:
    - Early post-operative DI occurs in the first 1-2 days and is linked to injury-related neuronal shock, during which no antidiuretic hormone (ADH) secretion takes place.
    - A recovery period follows, characterized by the inappropriate release of ADH (leakage from degenerating neurons). If not promptly recognized, this phase may lead to hyponatremia and typically lasts several days.

    - Permanent DI, indicating a lasting deficiency in ADH secretion due to damaged or absent neurons, usually becomes evident after approximately a week.

**Fluid management**

Acute DI can be managed with accurate fluid replacement alone; however, this has potential adverse effects, including hyperglycemia, intravenous line difficulties due to high infusion rates and urinary catheter leakage.

*Fluid type*

- IV sodium chloride 0.45% + glucose initially
- If serum sodium > 150 mmol/L: fluid type to be determined after discussion with Endocrinologist or intensivist, and depends on degree of hypernatremia, time over which this has developed and level of dehydration.
- If serum sodium < 135 mmol/L: sodium chloride 0.9% ± glucose 5%.
- Glucose content:
    - Glucose 5% (in addition to appropriate sodium chloride concentration) is appropriate for fluid rates up to approximately maintenance rate. Lower glucose concentration is required when fluid rate is high.
    - Sodium chloride 0.9% is available with glucose 5% or without glucose as standard ward stock.
    - Sodium chloride 0.45% + glucose 5% is standard ward stock.
    - Sodium chloride 0.45% + glucose 2.5% requires special order from stores.
    - Sodium chloride 0.225% is only available with glucose 3.75% and only stored in ICU.
- Maintenance IV potassium should be given but avoid adding to fluids that will be given at high or variable rates.

*Fluid rate* (when managing with fluid replacement alone), calculated hourly as:

- Volume of urine losses in previous hour, PLUS
- Insensible losses, calculated as 17 mL/m2/hour, PLUS
- Volume of other body fluid losses in previous hour, if applicable, PLUS
- A positive or negative adjustment to correct under- or overhydration over a set time period (often 12-48 hours).

    - Body weight and its change over time accurately reflects hydration status and should always be monitored in conjunction with fluid input and output.
    - Serum sodium > 150 mmol/L suggests underhydration; a positive adjustment may be needed.
    - Serum sodium < 135 mmol/L suggests overhydration; a negative adjustment/fluid restriction may be needed.
- Intravascular volume expansion, if required, should be achieved with sodium chloride 0.9% before commencing the above fluid management.

**ADH replacement**

ADH for therapeutic use is available in two forms:

- Aqueous argipressin (Pitressin®) 20 units/mL for continuous IV infusion
    - Commonly known as vasopressin
    - Requires intensive monitoring and should only be used in ICU and operating theatres.
    - Half-life 30 minutes, clinical duration of action 2-3 hours.
    - Titrate to urine output.
    - Should be used in acute post-operative DI, traumatic brain injury and brain death and with severe intercurrent illness.
- Desmopressin (Minirin®)
    - Half-life ~3 hours, duration of action 6-14 hours depending on formulation.
    - Should generally only be used in stable patients.
    - Oral 200 microgram tablets most used and are fully soluble in water, so can be dissolved to make smaller doses. Discard remainder and make up fresh for next dose.
    - Has an on-off effect, so dose determines duration of action, not degree of response.
    - The diuresis following the offset of action is often referred to as “breakthrough”.
    - Doses are not calculated by weight or body surface area (BSA), as there is significant dose variability between individuals, but there is a general relationship to body size.

- Generally, a small dose is given initially, with subsequent doses and frequency adjusted according to response.
- The decision to start desmopressin and the initial dose should always be discussed with the endocrinologist or intensivist.

**Table 5.** Desmopressin Formulations, Dose Equivalence, and Suggested Doses. Retrieved from The Sidney Children's Hospital Network. Central Diabetes Insipidus - Inpatient Management.; 2023. https://www.schn.health.nsw.gov.au/_policies/pdf/2023-084.pdf

| Form of desmopressin | Dose equivalent to 1 microgram parenteral | Age group | Starting dose | Common long-term dose ranges |
|---|---|---|---|---|
| **Oral**<br>200 microg tablet | 200 microg | <1 month<br>1 month-2 years<br>2-12 years<br>>12 years | 1-4 microg<br>10 microg<br>50 microg<br>100 microg | 5-50 microg/day<br>30-150 microg/day<br>100-800 microg/day<br>100-1200 microg/day |
| One tablet can be dissolved in 20 mL water to make 10 microg/mL solution. A standard dilution should be used consistently in individual patients. | | | | |
| **Intranasal**<br>100 microg/mL spray or drops | 10 microg (1 spray) | <1 month<br>1 month-2 years<br>2-12 years<br>>12 years | 0.1-0.5 microg<br>0.5-1 microg<br>1-2.5 microg<br>2.5-4 microg | 1.25-10 microg/day<br>1.25-10 microg/day<br>5-20 microg/day<br>5-20 microg/day |
| May need 1:10 dilution for small doses of nasal drop | | | | |
| **Parenteral**<br>(IV, IM or subcut)<br>4 microg/mL | 1 microg | <1 month<br>1 month-2 years<br>2-12 years<br>>12 years | 0.1 microg<br>0.1-0.4 microg<br>0.1-0.4 microg<br>0.5 microg | 0.2-1 microg/day<br>0.5-2 microg/day<br>0.5-2 microg/day<br>1-4 microg/day |
| Can be administered using an insulin syringe to enable accuracy with small doses | | | | |
| **Sublingual**<br>120 or 240 microg wafer | 120 microg | Generally only used temporarily if impaired enteral absorption. Use dose equivalent to effective oral dose. Smallest dose 60 microg (half wafer). | | |
| Not PBS-listed for DI | | | | |

**Low solute diet/thiazide diuretic**

- In cases of CDI in infants who rely on fluid for their nutrition, an endocrinologist may opt for a management approach involving a low-solute diet, like breastmilk, along with a thiazide diuretic instead of desmopressin. This strategy aims to minimize fluctuations in serum sodium levels. It's important to note that this decision should be made exclusively by the attending endocrinologist.
- Starting doses:
  - Chlorothiazide: 5-10 mg/kg/DAY in 2-3 divided doses per day
  - Hydrochlorothiazide: 1-2 mg/kg/DAY in 2-3 divided doses per day

**Treatment of hypernatremia**

- If serum sodium > 160 mmol/L, hypernatremia should be corrected slowly, unless there is clear evidence that hypernatremia has developed acutely (within 24 hours).
    - Fall in serum sodium should not exceed 0.5 mmol/L/hour.
    - Correction of dehydration over 48 hours is likely to achieve this.
    - Sodium chloride 0.9% is often the most appropriate rehydration fluid to achieve a safe rate of correction while serum sodium > 160 mmol/L.
    - Frequent serum sodium levels are required initially to establish a safe rate of correction.
- If serum sodium is falling too rapidly, fluid rate should be decreased and/or sodium content increased.

**Treatment of hyponatremia**

- Serum sodium < 135 mmol/L in the context of DI only occurs if there has been excess fluid intake and/or desmopressin/vasopressin administration.
- Fluid intake and desmopressin doses should therefore be reviewed if there is hyponatremia.
- Aim to correct the serum sodium level by no more than 0.5 mmol/L/hour to reduce the likelihood of osmotic demyelination.
    - This is usually achieved by fluid restriction.
    - Frequent serum sodium levels are required initially to establish a safe rate of correction.

**Fasting and surgery in patients with established diabetes insipidus**

For surgical procedures lasting less than 4 hours and not involving the pituitary gland:

- The patient should be scheduled as the first case.
- They can drink clear fluids to satisfy their thirst (or their regular fluid intake) until 1 hour before the surgery.
- The usual morning dose of desmopressin should be administered at least 1 hour before the procedure.
- Precise monitoring of fluid balance is essential during and after the operation.

- Intraoperative intravenous (IV) fluids should be limited to replacing insensible losses (17 mL/m2/hour) along with accurate replacement of fluid lost during surgery.
- The subsequent dose of desmopressin should be given after any unexpected excessive urination post-surgery.
- If the procedure experiences unanticipated delays or prolongation, a urinary catheter should be inserted, and urine output monitored.
    - If diuresis happens before anesthesia, an oral dose of desmopressin may be administered.
    - If diuresis occurs during the surgery, a vasopressin infusion should be initiated.
- For surgical procedures exceeding 4 hours in duration or those involving the pituitary gland, a vasopressin infusion is recommended. This infusion may commence either preoperatively in the intensive care unit (ICU) or intraoperatively once excessive urination occurs. In either case, it necessitates the use of a urinary catheter for meticulous urine output monitoring.

# Section 2.0 Drug Therapy in Central Diabetes Insipidus

This section comprises three subsections: the first contains the newly recommended drugs, the second covers drug modifications, and the third outlines the drugs that have been withdrawn from the market.

## 2.1 Additions

*After May 2020, there have been no central diabetes insipidus drugs that have received FDA or EMA approval.* Nevertheless, hydrochlorothiazide is also used in the management of central diabetes insipidus in infants and young children and registered in the SFDA. Hence, relevant information pertaining to this drug can be found below.[7]

### 2.1.1 Hydrochlorothiazide

**Table 6.** Hydrochlorothiazide Drug Information

| **SCIENTIFIC NAME Hydrochlorothiazide** | |
|---|---|
| **SFDA Classification** | Prescription |
| **SFDA Approval** | No |
| **US FDA** | No |
| **EMA** | No |
| **MHRA** | No |
| **PMDA** | No |
| **Indication (ICD-10)** | E23.2 |
| **Drug Class** | Antihypertensive |
| **Drug Sub-class** | Thiazide diuretic |
| **ATC Code** | C03AA03 |
| **Pharmacological Class (ASHP)** | 24:08.24.20 Thiazide Diuretics |
| **DRUG INFORMATION** | |
| **Dosage Form** | Tablet |
| **Route of Administration** | Oral use |
| **Dose (Adult) [DDD]*** | N/A |
| **Maximum Daily Dose Adults*** | N/A |
| **Dose (pediatrics)** | **Diabetes insipidus, central: Very limited data available: Infants and Children <3 years: Oral:** 1 to 2 |

| | |
|---|---|
| | mg/kg/day. Dosing based on retrospective descriptive analysis (n=13, age range: 0.5 to 27 months)[8] |
| **Maximum Daily Dose Pediatrics*** | N/A |
| **Adjustment** | Renal Impairment:<br>There are no dosage adjustments provided in the manufacturer's labeling; however, the following adjustments have been recommended:<br>• GFR ≥30 mL/minute/1.73 m2: No dosage adjustment necessary.<br>• GFR <30 mL/minute/1.73 m2: Use not recommended; use is contraindicated with anuria.<br>• **Hemodialysis, intermittent**: Not dialyzable; there are no dosage adjustments provided in the manufacturer's labeling; use not recommended.<br>• **Peritoneal dialysis:** There are no dosage adjustments provided in the manufacturer's labeling; use not recommended.<br>Hepatic Impairment:<br>There are no dosage adjustments provided in the manufacturer's labeling; however, use with caution and monitor for precipitation of hepatic coma. |
| **Prescribing edits*** | ST, AGE |
| **AGE (Age Edit):** Only studied in **infants and toddlers.** | |
| **CU (Concurrent Use Edit):** N/A | |
| **G (Gender Edit):** N/A | |
| **MD (Physician Specialty Edit):** N/A | |
| **PA (Prior Authorization):** N/A | |
| **QL (Quantity Limit):** N/A | |
| **ST (Step Therapy):** Can be used as an alternative if first-line agents have failed. | |
| **EU (Emergency Use Only):** N/A | |
| **PE (Protocol Edit):** N/A | |
| **SAFETY** | |

| | |
|---|---|
| **Main Adverse Drug Reactions (Most common and most serious)** | Frequency not defined:<br>Hypersensitivity angiitis, hypotension (including orthostatic), alopecia, skin rash, toxic epidermal necrolysis, urticaria, glycosuria, hypomagnesemia, abdominal cramps, anorexia, constipation, diarrhea, gastric irritation, nausea, vomiting, aplastic anemia, thrombocytopenia, anaphylaxis, dizziness, headache, paresthesia, restlessness, vertigo, asthenia, muscle spasm, blurred vision (transient), xanthopsia, acute kidney injury, fever.<br>Most serious / significant:<br>- Dermatologic toxicity<br>- Electrolyte disturbances<br>- Gout<br>- Hypersensitivity reactions (immediate and delayed)<br>- Ocular Effects |
| **Drug Interactions*** | Risk X interactions:<br>- Aminolevulinic Acid (Systemic)<br>- Bromperidol<br>- Dofetilide<br>- Levosulpiride<br>- Promazine |
| **Special Population** | Surgical patients: If given the morning of surgery, hydrochlorothiazide may render the patient volume depleted and blood pressure may be labile during general anesthesia. |
| **Pregnancy** | N/A |
| **Lactation** | N/A |
| **Contraindications** | Hypersensitivity to hydrochlorothiazide, any component of the formulation, or sulfonamide-derived drugs; anuria<br>**Note:** Although the FDA-approved product labeling states this medication is contraindicated in patients with hypersensitivity to sulfonamide- |

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|---|---|
| | containing drugs, the scientific basis of this cross-sensitivity has been challenged.<br>*Canadian labeling:* Additional contraindications (not in US labeling): Increasing azotemia and oliguria during treatment of severe progressive renal disease; breast-feeding. |
| **Monitoring Requirements** | Blood pressure; fluid intake and output; serum electrolytes; BUN, serum creatinine; skin to assess for photosensitivity and skin cancer; visual acuity, ocular pain. |
| **Precautions** | - Sulfonamide ("sulfa") allergy: The FDA-approved product labeling for many medications containing a sulfonamide chemical group includes a broad contraindication in patients with a prior allergic reaction to sulfonamides. There is a potential for cross-reactivity between members of a specific class (eg, two antibiotic sulfonamides). However, concerns for cross-reactivity have previously extended to all compounds containing the sulfonamide structure ($SO_2NH_2$). An expanded understanding of allergic mechanisms indicates cross-reactivity between antibiotic sulfonamides and nonantibiotic sulfonamides may not occur or at the very least this potential is extremely low. In particular, mechanisms of cross-reaction due to antibody production (anaphylaxis) are unlikely to occur with nonantibiotic sulfonamides. T-cell-mediated (type IV) reactions (eg, maculopapular rash) are less well understood and it is not possible to |

| | |
|---|---|
| | completely exclude this potential based on current insights. In cases where prior reactions were severe (Stevens-Johnson syndrome/TEN), some clinicians choose to avoid exposure to these classes.<br>- Adrenal insufficiency: Avoid use of diuretics for treatment of elevated blood pressure in patients with primary adrenal insufficiency (Addison disease). Adjustment of glucocorticoid/mineralocorticoid therapy and/or use of other antihypertensive agents is preferred to treat hypertension.<br>- Ascites due to cirrhosis: Use with extreme caution or avoid hydrochlorothiazide in the management of ascites due to cirrhosis; may lead to rapid development of hyponatremia when used in combination with spironolactone and furosemide.<br>- Bariatric surgery: Dehydration: Avoid diuretics in the immediate postoperative period after bariatric surgery; electrolyte disturbances and dehydration may occur. Diuretics may be resumed, if indicated, once oral fluid intake goals are met.<br>- Diabetes: Use with caution in patients with prediabetes or diabetes mellitus; may see a change in glucose control.<br>- Hepatic impairment: Use with caution in patients with severe hepatic dysfunction; in progressive or severe liver disease, avoid electrolyte and acid/base imbalances that might lead to hepatic encephalopathy/coma. |

| | |
|---|---|
| | - Hypercholesterolemia: Use with caution in patients with moderate or high cholesterol concentrations; increased cholesterol and triglyceride levels have been reported.<br>- Parathyroid disease: Thiazide diuretics reduce calcium excretion; pathologic changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed with prolonged use; should be discontinued prior to testing for parathyroid function.<br>- Renal impairment: Cumulative effects may develop, including azotemia, in patients with impaired renal function. Avoid in severe renal disease (ineffective).<br>- Systemic lupus erythematosus (SLE): May cause SLE exacerbation or activation. |
| **Black Box Warning** | N/A |
| **REMS*** | N/A |

**HEALTH TECHNOLOGY ASSESSMENT (HTA)**

After conducting a comprehensive analysis of several HTA bodies, such as NICE, CADTH, HAS, IQWIG, and PBAC, it was found that **none of them have provided specific recommendations regarding the use of *hydrochlorothiazide* for the treatment of central diabetes insipidus in pediatrics.** Despite this, hydrochlorothiazide has been available on the market for many years.

**Conclusion Statement – Hydrochlorothiazide**

Hydrochlorothiazide is mentioned in multiple guidelines as an alternative to first-line therapy in the management of central diabetes insipidus. Two retrospective studies were conducted to evaluate the use of hydrochlorothiazide in neonates and young children.

The first was a retrospective chart review of all infants and toddlers who were treated with thiazide diuretics for central DI at the Mayo Clinic between 1996 and

2014 (n=13). The study concluded that Thiazide diuretics seem to offer a safe and efficient treatment option for infants diagnosed with central diabetes insipidus[8].

The second was a retrospective chart review was conducted at Princess Margaret Hospital, Perth of neonates diagnosed with central DI and treated with hydrochlorothiazide, between 2007 and 2013. The study concluded that hydrochlorothiazide with low renal solute feed is a safe and effective treatment option in neonatal central DI[9].

Although the data is limited regarding its use for this indication (based on retrospective studies with a small sample size), the condition is not very common. Therefore, it is recommended to add hydrochlorothiazide to the CHI formulary as an alternative to first-line therapy.

### 2.2 Modifications

"Prior Authorization (PA)" and "MD" as prescribing edits for Dextrose, Sodium Chloride solutions should be removed since there is no need for prior authorization or for them to be prescribed by a specialty physician.

### 2.3 Delisting

There are no drugs that should be delisted from the SFDA drug list.

## Section 3.0 Key Recommendations Synthesis

- Although diabetes insipidus (DI) is an uncommon endocrine condition, failing to address it can negatively impact the patient's quality of life[5].
- The main causes are traumatic brain injuries (TBI), infections, hemorrhage affecting the posterior pituitary or hypothalamus, neurosurgical procedures, and the presence of tumors[5].
- In clinical practice, evaluating a patient involves performing a thorough medical history and physical examination, as well as verifying polyuria by assessing plasma osmolality and measuring the total 24-hour urine output[5].
- The water deprivation test (WDT) is the most commonly used test[4].
- Copeptin outperforms AVP as a diagnostic indicator due to its ability to provide results within two hours and its requirement for only a minimal plasma or serum sample of 50 µL[5].
- An alternative diagnostic method for CDI involves using an MRI scan of the pituitary gland[5].

- Managing acute DI solely through precise fluid replacement is an option, but it comes with potential drawbacks, such as the risk of hyperglycemia, challenges related to intravenous line placement due to the need for high infusion rates, and the possibility of urinary catheter leakage[6].
- The recommended therapy for CDI involves using desmopressin (DDAVP), a synthetic version of antidiuretic hormone (ADH)[5].
- Desmopressin (dDAVP) comes in multiple formulations, including injectable, oral, and nasal forms, to accommodate different administration methods[4].
- Oral desmopressin (dDAVP) is favored by the majority of patients due to its convenient administration and sustained efficacy, even in cases of nasal congestion resulting from infections[4].
- A somewhat unconventional strategy employed in the treatment of CDI and nephrogenic diabetes insipidus (NDI) includes the utilization of thiazide diuretics, which block the NaCl cotransporter in the distal convoluted tubule of the kidneys[5].

## Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Central diabetes insipidus report** and aims to provide recommendations to aid in the management of Central diabetes insipidus. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Central diabetes insipidus. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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# Section 6.0 Appendices

## Appendix A. Prescribing Edits Definition

**I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)**

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

| Prescribing edits Tools | Description |
|---|---|
| **AGE (Age):** | Coverage may depend on patient age |
| **CU (Concurrent Use):** | Coverage may depend upon concurrent use of another drug |
| **G (Gender):** | Coverage may depend on patient gender |
| **MD (Physician Specialty):** | Coverage may depend on prescribing physician's specialty or board certification |
| **PA (Prior Authorization):** | Requires specific physician request process |
| **QL (Quantity Limits):** | Coverage may be limited to specific quantities per prescription and/or time period |
| **ST (Step Therapy):** | Coverage may depend on previous use of another drug |
| **EU (Emergency Use only):** | This drug status on Formulary is only for emergency use |
| **PE (Protocol Edit):** | Use of drug is dependent on protocol combination, doses, and sequence of therapy |

## Appendix B. Central Diabetes Insipidus Scope

| 2020 | Changes | 2023 | Rationale |
|---|---|---|---|
| **Section 1.0 Central diabetes insipidus Clinical Guidelines** | | | |
| Society for Endocrinology Clinical Guidance for Inpatient management of cranial diabetes insipidus 2018 | N/A | | |
| Recommendations discussed in a review article published in the journal of clinical endocrinology in 2018 on Diagnosis and management of central diabetes insipidus in adults | Updated | Recommendations discussed in a review article published in the journal of clinical endocrinology in 2022 on Diagnosis and management of central diabetes insipidus in adults[4] | **Management of Fluid Intake**<br>• Evidence suggests that the management of fluid balance in hospitalized patients with diabetes insipidus during acute illness may be less than optimal, resulting in frequent occurrences of both hypernatremia and hyponatremia.<br>**Pharmacological Management of CDI**<br>• Due to its short duration of action, AVP is not suitable for therapeutic use in managing CDI.<br>• A synthetic analog called desmopressin (dDAVP) has been developed, extending its half-life from 5 minutes to 6 to 8 hours by removing the amino group of the cysteine amino acid.<br>• dDAVP can be administered two or three times daily, making it a viable therapeutic option.<br>• dDAVP is available in parenteral, oral, and nasal forms for various administration routes.<br>**Oral dDAVP**<br>• Most patients prefer oral desmopressin (dDAVP) over nasal spray because of its ease of |

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|---|---|---|---|
| | | | administration and continued effectiveness even during nasal congestion caused by infections.<br>**Nasal dDAVP**<br>• The earliest treatment for chronic CDI was the intranasal formulation of desmopressin (dDAVP).<br>• Patients with visual impairments may find the administration process challenging.<br>**Parenteral dDAVP**<br>• Desmopressin (dDAVP) can be administered either intravenously or subcutaneously.<br>**Other treatments**<br>• Carbamazepine directly stimulates V2 receptors, promoting the synthesis of aquaporin 2 expression, which in turn enhances water reabsorption.<br>• Chlorpropamide augments the action of AVP by increasing the expression of V2 receptors. However, its clinical utility is constrained by the risk of hypoglycemia.<br>• Clofibrate triggers the release of AVP from the neurohypophysis.<br>• None of these alternative agents possess similar effects to the mentioned ones.<br>**Management of Acute Diabetes Insipidus**<br>• The treatment approach involves minimizing renal water losses by administering dDAVP at a dosage of 1 to 2 µg through intramuscular or subcutaneous routes. In cases of transient CDI, a single dose may sometimes be adequate for subsequent administration. |

| | | | |
|---|---|---|---|
| | | | • Patients should be encouraged to drink water as per their thirst. In cases of cognitive impairment, appropriate intravenous fluids can be administered to maintain normal sodium levels (eunatremia).<br>• Acute central diabetes insipidus (CDI) is often temporary and may resolve after a single parenteral dose of desmopressin (dDAVP). Additional parenteral doses are necessary only if excessive urination persists.<br>• A recent survey conducted among pituitary endocrinologists indicates a strong consensus for the use of "on-demand" postoperative dDAVP rather than regular dosing.<br>• Continuous dDAVP treatment is only recommended if polyuria continues beyond 48 hours, as there is an occasional triphasic response.<br>**Management of Chronic Diabetes Insipidus**<br>• Symptomatic relief is typically rapid upon commencing dDAVP, and it offers effective long-term management of polyuria.<br>• If hypernatremic dehydration occurs, addressing electrolyte and fluid deficiencies is crucial.<br>• Mild hypernatremia (plasma sodium 145-148 mmol/L) can often be managed by ensuring free access to drinking water and encouraging oral intake. However, if the patient experiences hypotension or cognitive decline, |

| | | | |
|---|---|---|---|
| | | | intravenous administration of isotonic saline is recommended.<br>• Severe hypernatremia (plasma sodium >149 mmol/L) may necessitate the use of hypotonic fluids, such as nasogastric water or intravenous infusion of 5% dextrose in water.<br>**Management of CDI During Fasting, and Perioperative Care**<br>• The Society for Endocrinology guidelines emphasize the need for a collaborative plan involving the surgical, anesthetic, and endocrine teams regarding dDAVP and fluid replacement.<br>**Use of Alcohol in CDI**<br>• Patients with CDI are advised to exercise caution regarding alcohol consumption.<br>**Diabetes Insipidus in Pregnancy**<br>• Temporary diabetes insipidus associated with pregnancy is typically addressed using dDAVP, and this treatment can generally be discontinued within two months after giving birth.<br>**Adipsic Diabetes Insipidus**<br>- Treatment for adipsic diabetes insipidus (ADI) involves a twice-daily administration of dDAVP to regulate urinary output.<br>- A fixed fluid intake is also established, with the optimal volume typically determined through inpatient observations at the time of diagnosis. |
| Clinical guidelines for management of diabetes insipidus and syndrome of | N/A | | |

| | | | |
|---|---|---|---|
| inappropriate antidiuretic hormone secretion after pituitary surgery 2014 | | | |
| Review article published in Obstetrician & Gynecologist journal in 2017 about Diabetes insipidus in pregnancy. | N/A | | |
| Mini review about Diabetes insipidus--diagnosis and management. Hormone Research in Pediatrics published 2012 | N/A | | |
| | Missing | Review Article on Diabetes Insipidus: Pathogenesis, Diagnosis, and Clinical Management 2021[5] | • DI can be categorized into four primary types: central, nephrogenic, dipsogenic, or gestational. In adults, DI is typically characterized by a daily urine output exceeding 3-3.5 liters, accompanied by a urine osmolality of less than 300 mOsmol/kg.<br>• The primary categories of DI include central (neurogenic) and nephrogenic forms.<br>**Evaluation and differential diagnosis**<br>• In clinical practice, assessing a patient entails conducting a comprehensive medical history and physical examination, along with determining plasma osmolality and measuring the total 24-hour urine volume to confirm polyuria. Establishing baseline measurements of urine osmolality, plasma electrolytes, |

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| | | | and random serum values is also essential during the diagnostic process.<br>**Diagnosis**<br>• The indirect water deprivation test is used<br>• Copeptin is a recent clinical diagnostic marker for DI, and it is highly correlated with plasma arginine vasopressin (AVP).<br>• Both copeptin and AVP originate from the same precursor protein called pre-provasopressin.<br>• An MRI of the pituitary gland can also be used to diagnose CDI.<br>**Treatment**<br>• First-line treatments are available for both central and nephrogenic DI to help maintain fluid balance.<br>• A counterintuitive approach used to manage CDI and nephrogenic diabetes insipidus (NDI) involves the use of thiazide diuretics, which inhibit the NaCl cotransporter in the renal distal convoluted tubule.<br>• The preferred treatment for CDI is desmopressin (DDAVP), which is a synthetic form of ADH (antidiuretic hormone). |
| | Missing | CENTRAL DIABETES INSIPIDUS – INPATIENT MANAGEMENT PRACTICE GUIDELINE By the Sydney's children's Hospital Network 2023[6] | **Fluid management**<br>Acute DI can be managed with accurate fluid replacement alone; however, this has potential adverse effects, including hyperglycemia, intravenous line difficulties due to high infusion rates and urinary catheter leakage.<br>*Fluid type*<br>• IV sodium chloride 0.45% + glucose initially |

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| | | | • If serum sodium > 150 mmol/L: fluid type to be determined after discussion with Endocrinologist or intensivist, and depends on degree of hypernatremia, time over which this has developed and level of dehydration<br>• If serum sodium < 135 mmol/L*: sodium chloride 0.9% ± glucose 5%.<br>• Glucose content:<br>  ○ Glucose 5% (in addition to appropriate sodium chloride concentration) is appropriate for fluid rates up to approximately maintenance rate. Lower glucose concentration is required when fluid rate is high.<br>  ○ Sodium chloride 0.9% is available with glucose 5% or without glucose as standard ward stock.<br>  ○ Sodium chloride 0.45% + glucose 5% is standard ward stock.<br>  ○ Sodium chloride 0.45% + glucose 2.5% requires special order from stores.<br>  ○ Sodium chloride 0.225% is only available with glucose 3.75% and only stored in ICU.<br>• Maintenance IV potassium should be given but avoid adding to fluids that will be given at high or variable rates.<br>• Intravascular volume expansion, if required, should be achieved with sodium chloride 0.9% before |

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| | | | commencing the above fluid management.<br>**ADH replacement**<br>ADH for therapeutic use is available in two forms:<br>• Aqueous argipressin (Pitressin®) 20 units/mL for continuous IV infusion<br>o Commonly known as vasopressin o Requires intensive monitoring and should only be used in ICU and operating theatres.<br>• Desmopressin (Minirin®)<br>**Low solute diet/thiazide diuretic**<br>• In cases of central diabetes insipidus (DI) in infants who rely on fluid for their nutrition, an endocrinologist may opt for a management approach involving a low-solute diet, like breastmilk, along with a thiazide diuretic instead of desmopressin. This strategy aims to minimize fluctuations in serum sodium levels. It's important to note that this decision should be made exclusively by the attending endocrinologist.<br>• Starting doses:<br>o Chlorothiazide: 5-10 mg/kg/DAY in 2-3 divided doses per day<br>o Hydrochlorothiazide: 1-2 mg/kg/DAY in 2-3 divided doses per day<br>**Treatment of hypernatremia**<br>• If serum sodium > 160 mmol/L, hypernatremia should be corrected slowly, unless there is clear evidence that hypernatremia |

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| | | | has developed acutely (within 24 hours).<br>o Fall in serum sodium should not exceed 0.5 mmol/L/hour.<br>o Correction of dehydration over 48 hours is likely to achieve this.<br>o Sodium chloride 0.9% is often the most appropriate rehydration fluid to achieve a safe rate of correction while serum sodium > 160 mmol/L.<br>o Frequent serum sodium levels are required initially to establish a safe rate of correction.<br>• If serum sodium is falling too rapidly, fluid rate should be decreased and/or sodium content increased.<br>**Treatment of hyponatremia**<br>• Serum sodium < 135 mmol/L in the context of DI only occurs if there has been excess fluid intake and/or desmopressin/vasopressin administration.<br>• Fluid intake and desmopressin doses should therefore be reviewed if there is hyponatremia.<br>**Fasting and surgery in patients with established diabetes insipidus**<br>For surgical procedures lasting less than 4 hours and not involving the pituitary gland:<br>- The usual morning dose of desmopressin should be administered at least 1 hour before the procedure. |

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| | | | - Precise monitoring of fluid balance is essential during and after the operation.<br>- Intraoperative intravenous (IV) fluids should be limited to replacing insensible losses (17 mL/m2/hour) along with accurate replacement of fluid lost during surgery.<br>- The subsequent dose of desmopressin should be given after any unexpected excessive urination post-surgery.<br>  ○ If diuresis happens before anesthesia, an oral dose of desmopressin may be administered.<br>  ○ If diuresis occurs during the surgery, a vasopressin infusion should be initiated.<br>• For surgical procedures exceeding 4 hours in duration or those involving the pituitary gland, a vasopressin infusion is recommended. This infusion may commence either preoperatively in the intensive care unit (ICU) or intraoperatively once excessive urination occurs. In either case, it necessitates the use of a urinary catheter for meticulous urine output monitoring. |

## Appendix C. MeSH Terms PubMed

### C.1 Pubmed Search for Central Diabetes Insipidus

The following is the result of the PubMed search conducted for central diabetes insipidus guideline search:

| Query | Filters | Search Details | Results |
|---|---|---|---|
| **((((((((((((((Diabetes Insipidus, Neurogenic[MeSH Terms]) OR (Diabetes Insipidus Cranial Type[Title/Abstract])) OR (Diabetes Insipidus Primary Central[Title/Abstract])) OR (Diabetes Insipidus Secondary To Vasopressin Deficiency[Title/Abstract])) OR (Diabetes Insipidus, Central[Title/Abstract])) OR (Diabetes Insipidus, Cranial Type[Title/Abstract])) OR (Diabetes Insipidus, Neurohypophyseal[Title/Abstract])) OR (Diabetes Insipidus, Neurohypophyseal Type[Title/Abstract])) OR (Diabetes Insipidus, Pituitary[Title/Abstract])) OR (Diabetes Insipidus, Primary Central[Title/Abstract])) OR (Neurogenic Diabetes Insipidus[Title/Abstract])) OR (Neurohypophyseal Diabetes Insipidus[Title/Abstract])) OR (Pituitary Diabetes Insipidus[Title/Abstract** | Guideline, in the last 5 years | ("diabetes insipidus, neurogenic"[MeSH Terms] OR (("diabetes insipidus"[MeSH Terms] OR ("Diabetes"[All Fields] AND "Insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND "cranial type"[Title/Abstract]) OR (("diabetes insipidus"[MeSH Terms] OR ("Diabetes"[All Fields] AND "Insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND "primary central"[Title/Abstract]) OR ((("diabetes insipidus"[MeSH Terms] OR ("Diabetes"[All Fields] AND "Insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND ("neoplasm metastasis"[MeSH Terms] OR ("neoplasm"[All Fields] AND "metastasis"[All Fields]) OR "neoplasm metastasis"[All Fields] OR "secondaries"[All Fields] OR "secondary"[MeSH Subheading] OR "secondary"[All Fields])) AND "vasopressin deficiency"[Title/Abstract]) OR "diabetes insipidus central"[Title/Abstract] OR (("diabetes insipidus"[MeSH Terms] | 0 |

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| **])) OR (Vasopressin Defective Diabetes Insipidus[Title/Abstract])) OR (Vasopressin Deficiency[Title/Abstract])) OR (Central Diabetes Insipidus[Title/Abstract])** | | OR ("Diabetes"[All Fields] AND "Insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND "cranial type"[Title/Abstract]) OR "diabetes insipidus neurohypophyseal"[Title/Abstract] OR (("diabetes insipidus, neurogenic"[MeSH Terms] OR ("Diabetes"[All Fields] AND "Insipidus"[All Fields] AND "Neurogenic"[All Fields]) OR "neurogenic diabetes insipidus"[All Fields] OR ("Diabetes"[All Fields] AND "Insipidus"[All Fields] AND "Neurohypophyseal"[All Fields]) OR "diabetes insipidus neurohypophyseal"[All Fields]) AND "Type"[Title/Abstract]) OR "diabetes insipidus pituitary"[Title/Abstract] OR (("diabetes insipidus"[MeSH Terms] OR ("Diabetes"[All Fields] AND "Insipidus"[All Fields]) OR "diabetes insipidus"[All Fields]) AND "primary central"[Title/Abstract]) OR "neurogenic diabetes insipidus"[Title/Abstract] OR "neurohypophyseal diabetes insipidus"[Title/Abstract] OR "pituitary diabetes insipidus"[Title/Abstract] OR ((("vasopressin s"[All Fields] OR "vasopressine"[All Fields] OR "vasopressins"[MeSH Terms] OR "vasopressins"[All Fields] | |

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| | | OR "Vasopressin"[All Fields]) AND ("abnormalities"[MeSH Subheading] OR "abnormalities"[All Fields] OR "defects"[All Fields] OR "defect"[All Fields] OR "defect s"[All Fields] OR "defected"[All Fields] OR "defective"[All Fields] OR "defectively"[All Fields] OR "defectives"[All Fields])) AND "diabetes insipidus"[Title/Abstract]) OR "vasopressin deficiency"[Title/Abstract] OR "central diabetes insipidus"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter])) | |

## Appendix D. Treatment Algorithm

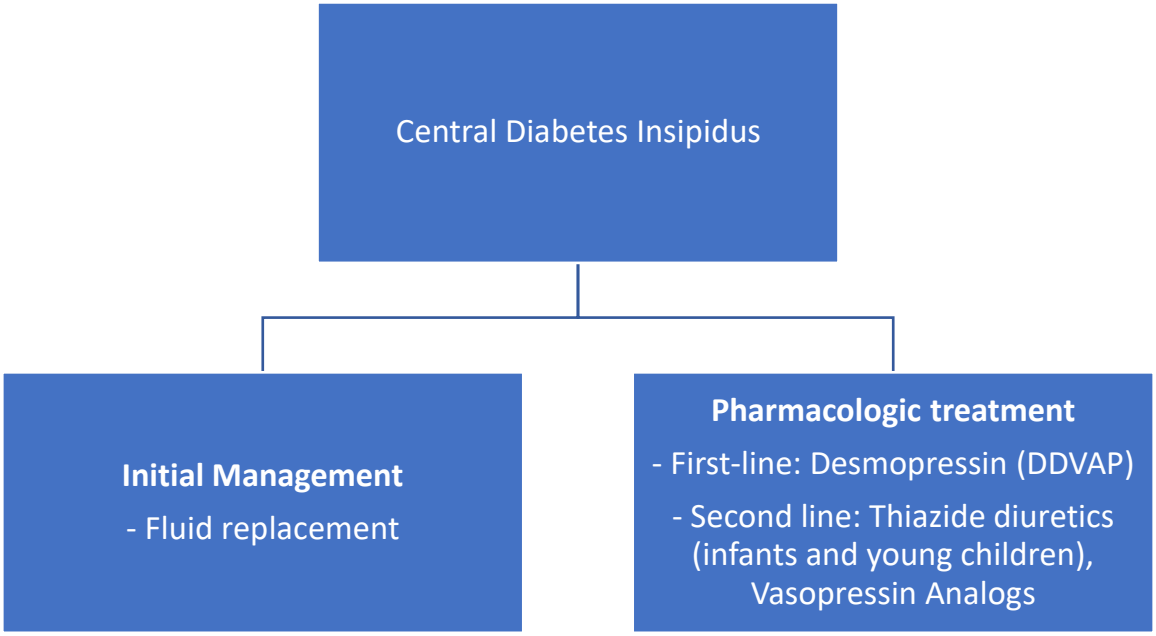


*Figure 1. Treatment Algorithm for the Management of Central Diabetes Insipidus*[4–6]