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Published in:
American Journal of Physiology: Renal Physiology

DOI:
10.1152/ajprenal.00339.2020

Publication date:
2020

Document version:
Accepted manuscript

Citation for published version (APA):

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A minireview of pharmacologic strategies used to ameliorate polyuria associated with X-linked nephrogenic diabetes insipidus

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Running title Treatment strategies in NDI

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Keywords AVPR2, Hypernatremia, vasopressin, water channels, V2 receptor

Abbreviations
Abstract

Nephrogenic diabetes insipidus (NDI) is characterized by renal resistance to the antidiuretic hormone arginine vasopressin (AVP) which leads to polyuria, plasma hyperosmolarity, polydipsia and impaired quality of living. Inherited forms are caused by X-linked loss-of-function mutations in the gene encoding the vasopressin 2- receptor (V2R) or autosomal recessive/dominant mutations in the gene encoding aquaporin 2 (AQP2). A common acquired form is lithium-induced NDI. AVP facilitates reabsorption of water through increased abundance and insertion of AQP2 in the apical membrane of the principal cells in the collecting ducts. In X-linked NDI, the V2R is dysfunctional, which leads to impaired water reabsorption. These patients have functional AQP2 and thus the challenge is to achieve AQP2 membrane insertion independently of the V2R. Current treatment is symptomatic, and is based on distally acting diuretics (thiazide, amiloride) and COX-inhibitors (indomethacin). The review covers published data from trials in preclinical in vivo models and few human intervention studies to improve NDI by more causal approaches. Promising effects on NDI in preclinical studies have been demonstrated by use of pharmacological approaches with secretin, Wnt5a, protein kinase A agonist, fluconazole, prostaglandin E2 EP2 and EP4 agonists, statins, metformin and soluble prorenin receptor agonists. In patients, only casuistic reports have evaluated the effect of statins, phosphodiesterase inhibitors (rolipram, sildenafil) or the guanylate cyclase stimulator, riociguat, without amelioration of symptoms. It is concluded that there is currently no established intervention that causally improves symptoms and quality of life in patients with NDI. There is a need to collaborate to improve study quality and conduct formal trials.

Introduction

Clinical features: Nephrogenic diabetes insipidus (NDI) can be acquired or congenital and is caused by an inability of the kidney to concentrate urine (Figure 1 depicts the normal physiological process). Congenital NDI is very rare, and most often caused by mutations in the AVPR2 gene located on the X-chromosome
encoding the vasopressin 2-receptor (V2R), but also individuals with aquaporin 2 (AQP2) mutations have
been described. These loss-of-function mutations result in NDI characterized by polyuria (often > 15L / day)
and excessive water intake, high plasma-sodium concentration and plasma osmolality in combination with
low urinary osmolality. Symptoms emerge early with failure to thrive. These patients are at high risk of
developing cognitive deficits caused by prevalent and recurrent hypernatremic dehydration episodes if
undiagnosed (32). The risk of irreversible neurological damage may be prevented if diagnosis is recognized
ey early (32, 34, 43). However, some patients develop learning or behavior problems and are diagnosed with
attention-deficit hyperactivity disorder or impaired concentration (23, 44). Patients with NDI often
experience nocturnal enuresis, incomplete voiding, interrupted night sleep and develop long term
complications including unilateral or bilateral hydronephrosis, enlarged bladder capacity with incomplete
bladder emptying and constipation (44). In cases where renal water loss is not sufficiently replaced by fluid
intake, the patients may develop severe hyperosmolar dehydration, hypotension, acute kidney failure,
cardiovascular symptoms, and hypovolemic shock. The changes in osmolality may cause irritability and
cerebral dysfunction, and in severe cases unconsciousness, seizure and coma (10). Although NDI caused by
a defect V2R presents a range of potential targets available for therapy, there is no curative
pharmacological therapy. Any successful treatment strategy to circumvent the V2R stimulation could
represent a noticeable improvement for patients with NDI. In the current minireview we focus on recent
advances in potential therapies for NDI. We restricted the review to in vivo data from preclinical animal
models of X-linked NDI and excluded in vitro studies and animal studies performed in central/pituitary
diabetes insipidus or lithium induced NDI in animals. In humans, we highlight the few available published
data from interventions in patients with V2R mutations and lithium-induced NDI.

Current symptomatic treatment guidelines

Current treatment of NDI includes both non-pharmaceutical and pharmaceutical interventions. Non-
pharmacologic interventions are pivotal to the management of NDI patients. Replacing water loss is critical
to avoid severe dehydration. Furthermore, salt- and protein restriction is recommended to reduce the osmotic load (7). Amiloride, thiazide diuretics and prostaglandin synthesis inhibitors individually or in combination are the most commonly used drugs for NDI (13) (Figure 3). Thiazides increased urinary osmolality and reduced diuresis in subjects with NDI (12). Thiazide diuretics induce a state of mild sodium depletion through inhibition of the sodium chloride co-transporter (Figure 3) in the distal nephron, which leads to an increased salt- and water reabsorption in the proximal tubules (16) mediated by stimulation of renin release and angiotensin II (ANGII) formation (26). This leads to a reduced amount of flow into the distal tubules thereby reducing diuresis. Furthermore, thiazides may confer additional antidiuretic effects through inhibition of carbonic anhydrase (Figure 3) in the proximal tubules and a subsequent reduction of GFR through tubulo-glomerular feedback (45). Amiloride inhibits sodium reabsorption through blocking the apical epithelial sodium channel, ENaC, (Figure 3) in the renal collecting duct principal cells, which, through a similar mechanism as for thiazides, may provide an ANGII-dependent anti-natriuretic effect in proximal tubules of NDI patients (1). Prostaglandin synthesis inhibitors, particularly indomethacin, have been reported to reduce urinary output especially in pediatric NDI patients and are often used in combination with thiazide diuretics (24, 28, 35, 36, 38, 46). The use of these drugs however, may be limited by side effects such as gastrointestinal bleeding and impaired kidney function and rarely renal failure (49). Thus, current interventions may reduce diureses, but do not significantly ameliorate the polyuric condition in NDI patients. Most patients will be treated with a combination of the drugs listed above during childhood, but a proportion of patients cease the treatment during adolescence without apparent worsening of their condition (44). It may be speculated that structural damage to the nephron associated with increased pelvic pressure and hydronephrosis contributes to loss of kidney function. There are limited reports of long-term renal outcomes in NDI patients, but two retrospective reviews of medical records in pediatric NDI patients found impaired renal function in a large proportion of patients (13, 44), one reporting a median eGFR 51mL7min (range 26-140) after a median follow-up of 9.5 years (44), and another study reporting 30% of patients with chronic kidney disease (CKD) stage 2 or greater (13).
Animal studies to treat NDI

Many in vivo and in vitro experimental approaches have been attempted to treat NDI (Figure 2+3). Especially X-linked NDI, caused by impaired V2R has been in focus, since AQP2 is expressed in the principal cells and could, theoretically, be inserted into the apical membrane, if the cyclic adenosine monophosphate (cAMP) pathway could be targeted. Available animal models, that mimic human X-linked NDI, have been challenging since V2R deficient male mice die within the first week after birth due to hypernatremic dehydration (50). To overcome this, mice with inducible V2R gene knockout during adult life, were developed (27). This murine model displayed the characteristic features of X-linked NDI; polyuria, polydipsia, significantly lower urine osmolality resistant to a selective V2R agonist (dDAVP) and morphological distention of the renal pelvis. Inner medullary collecting duct cells from these mice exhibited significant levels of the EP4 subtype of the prostaglandin E₂ (PGE₂) receptor. With the aim to bypass the defect V2R and stimulate a different Gs-coupled receptor, a compound selectively activating the EP4 PGE₂ receptor (ONOAE1-329) was tested. Result found an approximately 3-fold increase in urine osmolality 1 hour after injection and 50% lower cumulative urine output and water consumption, 6 hours after injection, despite absence of V2R (27). This provided proof-of-concept, that despite lower levels of AQP2 protein, there was sufficient available AQP2 in V2R-defect cells to recruit for insertion in the apical membrane and ameliorate the key manifestations of X-linked NDI. Chronic infusion of ONOAE1-329 for 3 weeks led to a reduction in urine output and water intake and a concomitant increase in urine osmolality, however, it was most pronounced after the first day of infusion which indicated, that PGE₂-EP4 receptor, could be a promising target for treatment of human patients. Using the same X-linked NDI murine model, Procino et al. (41), tested the effect of administration of secretin, a GI-peptide hormone coupled to Gs-dependent cAMP formation in combination with fluvastatin. They demonstrated that in secretin-infused X-linked NDI mice, a single injection of fluvastatin reduced urinary output about 90% and increased urine osmolality ~2 folds (41). Their hypothesis was based on previous studies showing that fluvastatin induced AQP2 membrane localization in vivo (39), and secretin receptor deficient mice displayed mild symptoms of
suggesting that secretin might exhibit antidiuretic effect. Another approach to study X-linked NDI in animal experiments was by disabling the V2R by administration of the V2R antagonists, tolvaptan (33) or OPC-31260(21, 31). Tolvaptan infusion induced significant diuresis and hypoosmotic urine making this model suitable for further studies. Using this strategy, Ando et al. (3) tested whether targeting and increase of intracellular calcium signaling by Wnt5a could be a target for treatment of X-linked NDI. In this tolvaptan-induced X-linked NDI model, administration of intraperitoneal Wnt5a increased urine osmolality and attenuated the effects of tolvaptan. Moreover, compared to tolvaptan-treated mice, control mice and tolvaptan plus Wnt5a-treated mice accumulated AQP2 in the apical membrane. In another study, administration of FMP-API-1, a direct activator of protein kinase A (PKA) (A-kinase Anchoring Protein (AKAPs)-PKA disruptors), which dissociate the binding of AKAPs and PKA R subunits) were tested in the tolvaptan NDI mouse model(2). This novel compound significantly attenuated the effect of tolvaptan, and increased urine osmolality in NDI mice compared to controls (from -500 mOsm/kgH2O in tolvaptan treated vs. -1000 mOsm/kgH2O in tolvaptan+FMP-API-1 treated) (2). Vukicevic et al. (48) recently performed another interventional study to test whether administration of fluconazole in V2R antagonized mice attenuated symptoms of NDI. This approach was based on their previous study which identified the antifungal drug fluconazole as a candidate for AQP2 modulation, based on screening a library of 17,700 molecules in a cell-based assay (8, 48). Fluconazole increased plasma membrane localization of AQP2 in the absence of AVP (48) caused by alterations in the phosphorylation status and ubiquitination and due to inhibition of RhoA. In the subsequent animal experiment with tolvaptan-induced diuresis, administration of fluconazole significantly reduced urinary output (~1.5 ml/day in NaCl treated vs. ~1.0 ml/day in fluconazole treated mice) and increased urinary osmolality (~750 mOsm/kgH2O in NaCl treated vs. ~1250 mOsm/kgH2O in fluconazole treated mice)(48). Administration of OPC-31260 is another approach to block the V2R and create an in vivo experimental model mimicking human X-linked NDI (21, 31). Using this compound in rats, Olesen et al(37) found, that butaprost, a stimulator of the E-prostanoid receptor (EP2) significantly reduced urine volumes to 56% and 62% (day 1 and 2, respectively) in butaprost treated mice compared to control
values and increased urine osmolality (~200 vs ~400 mOsm/kgH₂O, OPC vs. OPC+butaprost, respectively) representing an alternative mechanism to increase kidney concentrating ability. In another study, administration of OPC-31260 in mice also induced symptoms of NDI that were attenuated by a recombinant histidine-tagged soluble (pro)renin receptor (sPRR-His) treatment, with a decrease of urinary output (~ 4ml/day vs ~2.8ml/day in OPC vs OPC+sPRR-HIS, respectively) and increase in urinary osmolality (~ 2400mOsm/kgH₂O vs 1200mOsm/kgH₂O in OPC vs OPC+sPRR-HIS, respectively) after three days of treatment (29). (29) Efe et al. (17) performed a comprehensive study of the therapeutic effect of metformin, a stimulator of 5’AMP-activated protein kinase (AMPK), in 2 models of X-linked NDI; V2R blockade by tolvaptan in rats and knockout of the V2R in mice. Tolvaptan decreased urine osmolality (from 2,108 ± 134 mOsM to 1.303 ± 127 mOsM), which was restored to baseline levels upon treatment with metformin (2,335 ± 273 mOsM). These results were in accordance with an increased urine osmolality within 2 hours, persisting for 12 hours in metformin-treated V2R KO mice (17). In conclusion, promising effects on NDI in preclinical studies have been demonstrated by use of pharmacological approaches with secretin, Wnt5a, PKA agonist, fluconazole, PGE₂ EP2 and EP4 agonists, statins, metformin and soluble prorenin receptor agonists.

**Experimental studies in humans**

There is a remarkable scarcity of published attempts to translate *in vitro* findings and preclinical animal studies into clinical settings (Figure 2). The rarity of the disease poses a major challenge to gather a sufficient number of patients to perform a clinical trial.

**Drugs increasing the concentration of cyclic adenosine monophosphate/cyclic guanosine monophosphate:**

Before the exact intracellular mechanisms involved in V2R activation were known, interventions aiming to increase cAMP levels were attempted. In 1972, Jones et al. treated three pediatric patients with intravenous boles of cAMP 1-3 mg/kg. Although this led to a transient reduction of diuresis, which was likely secondary to a drop in blood pressure, it did not impact urinary osmolality or urinary sodium
concentration (25). In 1990, treatment with increasing doses of the phosphodiesterase type 3 inhibitor Rolipram for 7 days in two adult male patients with NDI showed no effect on urinary osmolality or free water clearance (6). A case report of a 4½ year old male pediatric patient with X-linked NDI showed a beneficial effect of the phosphodiesterase type 5 inhibitor, sildenafil, which normalized plasma sodium levels and plasma osmolality and reduced the 24-hour diuresis by 50% compared to standard treatment with hydrochlorothiazide-amiloride and indomethacin after 10 days of treatment (4). This promising observation could not be reproduced in an open-label intervention study including two adult male patients with NDI due to an AVPR2 mutation (22). In a cross-over design sildenafil was tested followed by the soluble guanylate cyclase stimulator, riociguat. The treatments had no effect on baseline diuresis or the urine concentration ability after 7 days of treatment, despite increases in cyclic guanosine monophosphate (cGMP)(22). Similarly, a cross-over study with high doses of sildenafil (100-200 mg/day) in combination with calcitonin in 4 children and young adults with NDI found no effect on 24-hour urinary volumes (unpublished, clinicaltrials.gov: NCT00478335). A study in healthy volunteers corroborated these negative findings. Individuals were treated with tolvaptan to induce diuresis. Sildenafil did not affect AVP-independent urinary concentration ability (5).

Statins: Evidence from in vitro and animal studies indicate a potential effect on AQP2 abundance in the apical membrane of the principal cells in the renal collecting ducts by cholesterol lowering drugs (statins) (reviewed in (9)). In a study of 37 subjects with hypercholesterolemia and normal renal function, simvastatin treatment for 12 weeks resulted in a rapid (within one week) and sustained increase in urinary AQP2 excretion and a simultaneous increase in urinary osmolality. The increased urinary AQP2 excretion was also observed in subjects on long-term simvastatin treatment (42). In a study of 12 healthy volunteers, 40 mg of simvastatin surprisingly reduced baseline urinary osmolality after one week of treatment (760 (353–937) vs. 388 (187–388) mOsm/kg, p=0.02) despite standardized water intake before the trial date. On the contrary, after water loading, the minimal urinary osmolality was slightly, but significantly higher after
simvastatin (70 (61–89) vs. 85 (65–96) mOsm/kg, p=0.05) (5). These contradicting results highlight the complexity of renal water handling *in vivo*. In lithium-induced NDI, a cross-sectional study of 71 lithium-users showed an association between the use of statins and urinary osmolalities above 300 mOsm/kg, which was present in 17/17 statin users compared to 43/54 statin non-users (p=0.055). The overall urinary osmolality was similar between the two groups (18). These results prompted the initiation of an ongoing randomized, placebo-controlled clinical trial of atorvastatin 20 mg/day in 60 patients with indications of lithium-induced NDI defined as a urinary osmolality < 600 mOsm/kg after 10 hours of water deprivation (19). The results of this trial are yet to be published. Only one report has described the use of fluvastatin titrated to 80 mg/day in a patient with X-linked NDI due to a V2R mutation. While there was an apparent increase in AQP2 abundance in urinary exosomes after fluvastatin, there was no effect on urinary output or urinary osmolality after 60 days of treatment (40).

Acetazolamide: Attention has been drawn towards a role of the carbonic anhydrase inhibitor acetazolamide in the treatment of lithium-induced NDI, which was sparked by the observation, that thiazides could reduce diuresis in thiazide sensitive sodium chloride cotransporter (NCC)-knockout mice, presumably through inhibition of carbonic anhydrase in the proximal tubules (45). The first report of the use of acetazolamide in a patient with NDI was a 49-year old male with NDI due to long-term lithium treatment. Due to large diuresis and inability to take in fluids orally in the postoperative phase after an intracerebral operation, acetazolamide was initiated and led to a marked decrease in diuresis, normalization of plasma sodium and increase in urinary osmolality (20). A similar promising effect of acetazolamide was found in a patient with lithium-induced NDI during hospitalization due to a bowel obstruction (30). On the contrary, a study of six patients with lithium-induced NDI failed to reproduce these findings (14). In this study, there was a high frequency of side-effects associated with acetazolamide treatment including impaired renal function. In the context of hereditary NDI, results from lithium-induced NDI are probably not directly applicable, since it has been hypothesized, that acetazolamide works through attenuation of the lithium-
induced increase in prostaglandin E\(_2\) (15). Indeed, no studies have reported the use of acetazolamide in X-linked NDI (Figure 2).

**Metformin:** Despite indications from mouse studies of a potential effect of metformin to increase urinary osmolality in AVPR2-knockout mice (17), very sparse data exist regarding this effect in NDI patients. Only one study has been registered in clinical trial registries (clinicaltrials.gov: NCT02460354). This study aimed to include 20 NDI patients with an AVPR2 mutation in an open-label, single-group trial investigating the effect of metformin 500 mg, once daily, on urinary osmolality and diuresis. The study was terminated after two patients completed, due to a lack of effect. In summary, published studies regarding treatment of NDI patients are either case reports or include very few participants and promising preclinical results have not been reproducible in subsequent studies.

**Challenges for human studies and future strategies**

Experimental animal models mimicking human X-linked NDI have been employed, to test ability of pharmacological compounds, to ameliorate the symptoms of NDI. However, it is necessary to consider potential side effects of the treatment strategies when transferring to a human setting. Few studies were performed using pharmacological therapy appropriate for direct translation into human interventional studies. Translation of preclinical data into clinical trials has been sparse and with predominantly negative results (Figure 2). There is an unmet need for improved treatment regimens in NDI. In recent years, there has been a global interest in repurposing previously approved drugs for new indications, which may significantly reduce both costs and efforts associated with drug approval (47). In that respect, the animal studies using fluconazole may hold promise of feasible interventional trials in patients with congenital NDI. Likewise, conclusive results regarding effects of metformin in the treatment of hereditary NDI are lacking. An interesting approach, which is currently unexplored in humans, would be to combine treatments directed at different targets. For example, a combination of V2R independent drugs i.e. secretin or EP4-PGE2 receptor agonists combined with a statin or fluconazole could have an additive effect. An important
The challenge in NDI research is gathering the sufficient number of participants to perform conclusive clinical trials. Furthermore, consideration should be paid to selecting sufficiently high dosages of drugs, fully or partially eliminated by filtration, due to the observation that NDI patients often have an elevated renal plasma clearance. We encourage international collaborations in future interventional trials. In light of promising results from pre-clinical studies, a dedicated effort to perform sufficiently powered translational clinical trials, may provide the long-awaited break-through in the management of NDI patients.

**Disclosures**

None

**Author contributions**

GH and LAM drafted manuscript. GH prepared figures. CB and BLJ edited and revised the manuscript.

**Funding**

Work in the authors lab is supported by Odense University Hospital; The Novo Nordisk Foundation, Karen Elise Jensen Foundation and The Danish Research Fund-Health Science.

**Figure legends**

Figure 1: Schematic presentation of the AVP-mediated trafficking of AQP2 in the principal cells of the collecting ducts. Binding of AVP to the G protein coupled, vasopressin-2 receptor (V2R) located in the basolateral membrane, stimulates the release of GαS, which in turn increases the conversion of ATP to cAMP. Increased levels of cAMP activate PKA, which subsequently phosphorylates several residues on the c-terminus of AQP2 and enables trafficking and insertion of AQP2 into the apical membrane and facilitates water diffusion along concentration gradients. Water exits the cell by AQP3 and AQP4 located in the basolateral membrane.
Figure 2: Overview showing recent publications about potential treatment strategies for congenital nephrogenic diabetes insipidus. X-axis depicts years. Y-axis depicts clinical trials in patients with X-linked NDI and in vivo studies in animal model with X-linked NDI induced by V2R blockade or V2R KO. Although multiple investigative drugs have been examined in mice models with promising data to support AVP independent AQP2 activation, the progression into clinical trials are sparse.

Figure 3: Left panel: Current treatment is symptomatic and based on distally acting diuretics (thiazide, amiloride) that enhance proximal tubular reabsorption and COX-inhibitors like indomethacin. Right panel: Potential treatment strategies and proposed mechanism of action.


Figure 1
Fluconazole reduced urinary output in tolvaptan treated mice.⁴⁸

AKAPs-PKA disruptors significantly attenuated the effects of tolvaptan, a V2R antagonist in mice.²

A selective EP4 PGE2 receptor agonist attenuated polyuria in mice with inducible deletion of V2R and restored renal AQP2 expression.⁴²

Metformin increased AQP2 in the V2R KO mice similar to the tolvaptan-treated rats.¹⁷

Wnt5a improved urine concentration ability in tolvaptan-induced V2 blockade.³

Administration of secretin and fluvastatin in combination ameliorated polyuria in V2R mutant mice.⁴¹

Fluvastatin in a patient with X-linked NDI increased uAQP2, but it was not accompanied by a reduction of diuresis or an increase of urine osmolality.⁴⁴

Sildenafil reduced urine volume and p-sodium and increased urine osmolality and AQP2 in a boy with X-linked NDI.⁴

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Neither sildenafil nor riociguat had any effect on daily urine output or urine concentration ability during water deprivation in two adult male patients with X-linked NDI.²²

Butaprost, a EP2 stimulator reduced urine volume and increased urine osmolality in rats with V2R blockade using OPC-31260.³⁷

In vivo experiments in NDI-models

Clinical trials in NDI

No effects were observed in two male X-linked NDI patients treated with Rolipram, a cyclic AMP-phosphodiesterase isoenzyme type III.⁶

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Fluconazole: Reduces RhoA activity and F-actin, thereby preventing the physical barrier that usually prevents AQP2 bearing vesicles from reaching the plasma membrane.

AKAPs-PKA disruptors: Dissociate binding of AKAPs and PKA subunits, increase PKA activity, which leads to AQP2 phosphorylation, trafficking, and water reabsorption.

Metformin: Stimulates the catalytic subunits AMPK, a serine/threonine kinase, which facilitates phosphorylation of AQP2 and UT-A1

Soluble (pro)renin receptor: Binds FZD8 which activates the Wnt/β–catenin pathway and increase cAMP accumulation which leads to enhanced AQP2 expression.

Wnt5a: Activates the calcium/calmodulin/calcineurin signaling pathway, thereby regulating phosphorylation, trafficking and protein expression of AQP2

Secretin and fluvastatin: Increase cAMP and AQP2 abundance. Fluvastatin induce AQP2 membrane accumulation possible through reduced prenylation of RhoA and Rab5

E-prostanoid receptor agonists: Activates the Gs-coupled EP4 and EP2 PGE2 receptor thereby increasing cAMP levels

Sildenafil or riociguat: A phosphodiesterase type 5 inhibitor and sGC stimulator that increase cGMP and thereby PKA and PKG activity

Rolipram: inhibitors of cyclic AMP-phosphodiesterase, thereby increasing cAMP and subsequently PKA
A minireview of pharmacologic strategies used to ameliorate polyuria associated with X-linked nephrogenic diabetes insipidus

METHODS

The review summarizes primarily on in vivo data from preclinical animal models of X-linked NDI and published data from intervention studies in patients with V2R mutations and lithium-induced NDI.

RESULTS

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CONCLUSION

There is currently no established intervention that causally improves symptoms and quality of life in patients with NDI. There is a need to collaborate and translate findings from in vivo experiments into human interventional trials.