Potential clinical applications of current and future oral forms of desmopressin (Review)

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Abstract. Desmopressin is a synthetic analogue of vasopressin and a selective vasopressin receptor 2 agonist. It was first synthesised in 1967 and utilised for its antidiuretic properties. It is also used in bleeding disorders to enhance clotting. Other potential uses of the drug have been reported. The present review aims to provide a broad overview of the literature on potential further uses of oral forms of desmopressin. Key therapeutic areas of interest were identified based on known physiological activities/targets of desmopressin or reports of an effect of desmopressin in the literature. The feasibility of adequate dosing with oral forms of the drug was also considered. Systematic literature searches were carried out using the silvi.ai software for the identified areas, and summaries of available papers were included in tables and discussed. The results of the searches showed that desmopressin has been investigated for its efficacy in a number of areas, including bleeding control, renal colic, the central nervous system and oncology. Evidence suggests that oral desmopressin may have the potential to be of clinical benefit for renal colic and bleeding control in particular. However, further research is needed to clarify its effect in these areas, including randomised controlled studies and studies specifically of oral formulations (and doses). Further research may also yield findings for cancer, cognition and overactive bladder.

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1. Introduction

Desmopressin is a vasopressin (AVP) receptor 2 (V2) agonist, first synthesised in Prague in the late 1960s by Zaoral *et al* (1). At the time, the objective was to develop an analogue of the native vasopressin hormone that could be used in the treatment of central diabetes insipidus, avoiding the, mainly V1-mediated, side effects of vasopressin treatment relating to its pressor effects, while maintaining or improving upon its antidiuretic effects. Among several analogues produced and evaluated, desmopressin (1-deamino-8-D-arginine vasopressin) proved to be a triumph in achieving the required efficacy and tolerability profile: 'Rarely in pharmacology is an agent produced that so specifically enhances the desired effect and simultaneously decreases the side effect' (2).

To this day, desmopressin is used widely for central diabetes insipidus and in other conditions requiring antidiuretic treatment, including nocturnal enuresis (bedwetting), idiopathic nocturnal polyuria and nocturia (nocturnal voiding) (3).

In the 1970s, a new indication came to light when intravenous administration of high doses of desmopressin was found to raise levels of the clotting factor Factor VIII in healthy volunteers and in patients with mild-to-moderate haemophilia A and von Willebrand's disease (VWD). These are both inherited bleeding disorders characterised by low levels of Factor VIII or von Willebrand factor (a carrier for Factor VIII), leading to impaired blood clotting (4,5). Desmopressin became, and remains, a valuable addition to the treatment armamentarium

for these conditions, helping to prevent bleeding episodes via intravenous or intranasal administration (6).

While these uses of desmopressin are well established, there has also been a significant number of reports of clinical benefit in other diverse clinical areas, including distinct but related areas within urology and haematology, as well as completely different disciplines such as oncology and psychiatry/cognition.

In this review, we explore potential for further clinical applications of current and possible future forms of oral desmopressin. We focus on oral formulations, rather than intravenous, subcutaneous or intranasal, because they have the advantages of being easily administered in the home or outpatient setting, are more child friendly, and data suggest that side effects are reduced with oral formulations compared with intranasal ones (7). Because the available oral formulations [tablet and orally disintegrating tablet (ODT)] are used at bioequivalent doses, we refer to them collectively as oral desmopressin. The ODT dissolves under the tongue in a few seconds, whereas the tablet is swallowed.

Desmopressin dosing, formulations and target tissues. The widespread distribution of V2 receptors in the human body (Fig. 1) is itself suggestive that a V2 agonist is likely to have diverse physiological and clinical effects. However, there are two important questions that need to be considered when determining the potential for oral desmopressin to be beneficial in relevant clinical conditions. First, is desmopressin able to reach and/or affect each of the target organs of interest when administered orally? Second, can desmopressin be administered orally at a dose which is both effective and has an acceptable safety profile. Existing oral formulations of desmopressin have low bioavailability. It is currently available as a tablet and as an orally disintegrating (ODT)-see Table I for an overview of dose comparisons across formulations. The ODT has greater bioavailability than the tablet, enabling lower dosing. The ODT formulation has a maximum daily dose of 240 μg for enuresis, while in adults with idiopathic nocturnal polyuria (nocturia) the maximum daily dose is lower and sex-specific at 25 μg for women and 50 μg for men (3). Doses differ in other indications. All formulations, however, demonstrate increased risk of side effects with increasing dose, particularly in older age, when hyponatraemia becomes more likely (8). For current indications requiring higher doses, administration is limited to single or few dosages that are used for specific one-off events, such as surgery or trauma in patients with mild to moderate haemophilia A and VWD.

Pharmacokinetic data indicate that the desmopressin tablet and ODT tablet formulations have a linear dose relationship as follows: 60, 120, 240 and 360 μg ODT correspond to 0.1, 0.2, 0.4 and 0.6 mg tablet, respectively. Regarding bioequivalence of the two oral formulations, all regulatory approvals were based upon bioequivalence studies which showed that lower dosing of the ODT is required due to its higher bioavailability (0.25 vs. 0.16%, as shown in Table I). In addition, it has been proposed that there are some clinically relevant differences between the two oral formulations in terms of their PK/PD profile, such as more predictable dosing (9) and lower food interaction with the ODT (10,11).

A conversion factor between intravenous and oral desmopressin has not been defined; however, the bioavailability of oral desmopressin is approximately 100 times lower than that of IV desmopressin (12). Thus, the IV equipotent dose to 200 μg oral desmopressin would be around 2 μg (13). Each formulation delivers the adequate dose for the approved indications.

We have selected a subset of target organs/tissues for discussion (Table II) based on V2 agonism effects that are well-recognised and understood (in blood and kidney), or on studies in the literature suggesting that desmopressin may be of interest in these areas (ureter, CNS, oncology).

2. Methods

Systematic literature searches of PubMed-indexed literature were conducted using the Silvi.ai software (https://www.silvi.ai/) in each of the potential new areas of interest identified: bleeding control, renal colic, CNS and oncology. Details of the searches are provided in Table III.

Relevant studies in humans, published in English, were included and a table of publications compiled for each area. A small number of additional relevant studies were found during PubMed searches/citation chasing. Summary tables of relevant studies, their characteristics and findings were developed to summarise the literature in therapeutic areas where oral desmopressin use may be feasible, and studies were categorised according to whether findings were supportive of the use of desmopressin or not. Although the literature searches were systematic, the literature cited in this report is not exhaustive due to the wide remit of interest and the fact that some publications could not be accessed without payment-articles were paid for only in the renal colic and CNS searches as these retrieved fewer results. This review therefore provides a broad overview of the evidence across multiple clinical areas. For bleeding disorders, publications specifically of relevance to low-dose desmopressin were sought, since there is a huge body of literature on the approved use of high dose (intravenous/subcutaneous) desmopressin in bleeding disorders and summarising this literature was deemed out of scope because our interest is specifically in oral desmopressin and possible new uses of these formulations. Similarly, for oncology, the doses used in human studies have been above those achievable with oral formulations and only a brief overview of the literature is given.

3. Results of literature review and discussion of findings

Desmopressin and bleeding disorders. Desmopressin (IV, subcutaneous or intranasal) is indicated for use in bleeding disorders (VWD and mild-to-moderate haemophilia type A), with a long history of clinical usage and many publications confirming its efficacy (6,14). Although IV desmopressin is recommended before surgery or for treating severe haemorrhages because very consistent responses are required in these situations, subcutaneous desmopressin can be self-administered and can therefore be used at home to prevent or treat minor bleeding episodes and in women with VWD who have excessive bleeding at menstruation (15). In bleeding disorders, desmopressin is used at high doses (0.3-0.4 μg/kg body weight IV) to increase Factor VIII:C and Factor VIII:Ag in patients with mild to moderate haemophilia A or VWD who are undergoing surgery or following trauma (16). In order to achieve

Table I. Dose comparison of different formulations of desmopressin.

Parameter	IV injection (solution)	Intranasal spray	Tablet	ODT
Bioavailability, % (SD or 95% CI)	N/A	6.00(±2.29)	0.16(±0.17)	0.25 (95% CI, 0.21-0.31)
Equivalent doses[a], μg	N/A	2.5	100	60
	<0.5	5	200	120
	<1	10	400	240

[a]Note that there appear to be some age-related differences in equivalence in small children (10). The table is based on Ferring data on file from three studies (internal identifiers: CS004, RG84063-102 and 45A02/48) (114). IV, intravenous; N/A, not applicable; ODT, orally disintegrating tablet.

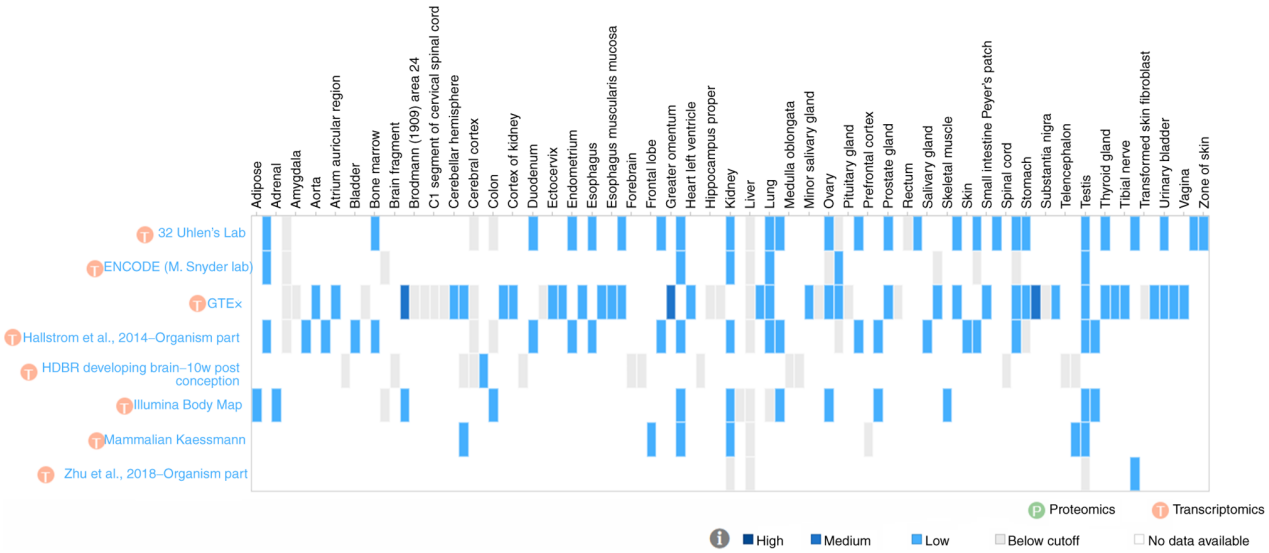

Figure 1. Sites tested for arginine vasopressin receptor 2 expression in human tissue. The figure shows alternate site labels only. The full listing of sites is as follows (asterisks denote detection of vasopressin receptor 2 transcript in at least one study) (113): Adipose*, adipose tissue*, adrenal*, adrenal gland, amygdala, animal ovary*, aorta*, appendix*, atrium auricular region*, basal ganglion (developing), bladder*, blood, bone marrow*, brain, brain fragment (developing), breast*, Brodmann (1909) area 24, Brodmann (1909) area 9, C1 segment of cervical spinal cord, caudate nucleus, cerebellar hemisphere*, cerebellum*, cerebral cortex, choroid plexus (developing)*, colon*, coronary artery*, cortex of kidney*, diencephalon, duodenum*, Epstein-Barr virus-transformed lymphocyte, ectocervix*, endocervix*, endometrium*, esophagogastric junction*, esophagus*, esophagus mucosa*, esophagus muscularis mucosa*, fallopian tube*, forebrain (developing), forebrain and midbrain (developing), frontal lobe*, gall bladder*, greater omentum*, heart*, heart left ventricle*, hindbrain (developing), hippocampus proper, hypothalamus, kidney*, leukocyte, liver, lower leg skin*, lung*, lymph node*, medulla oblongata (developing), midbrain (developing), minor salivary gland*, nucleus accumbens, ovary*, pancreas*, pituitary gland, placenta*, prefrontal cortex, prostate*, prostate gland*, putamen, rectum, saliva-secreting gland*, salivary gland*, sigmoid colon*, skeletal muscle*, skeletal muscle tissue*, skin*, small intestine*, small intestine Peyer's patch*, smooth muscle tissue*, spinal cord (developing), spleen*, stomach*, subcutaneous adipose tissue*, substantia nigra, suprapubic skin*, telencephalon (developing), temporal lobe (developing), testis*, thyroid*, thyroid gland*, tibial artery*, tibial nerve*, tonsil*, transformed skin fibroblast, transverse colon*, urinary bladder*, uterus*, vagina*, vermiform appendix*, and zone of skin*. ENCODE, The Encyclopedia of DNA Elements; GTEx, Genotype-Tissue Expression; HDBR, Human Developmental Biology Resource; w, weeks.

a bioequivalent dose in an average adult, approximately 5,000-7,000 μg desmopressin ODT would be needed.

Intranasal administration is also indicated for patients with these bleeding disorders (17) when they are undergoing surgery, following trauma or for other bleeding episodes such as menorrhagia and epistaxis (nosebleeds). The intranasal spray may be used (300 μg) half an hour before surgery or at bleeding. Using bioequivalence data (Table I), approximately 7,200 μg oral desmopressin ODT would be required to achieve the same dosing as recommended for adults using the intranasal spray (i.e. 10 μg intranasal=240 μg ODT, so 300 μg intranasal=7,200 μg ODT). Currently, the maximum strength of oral ODT is 240 ug, meaning that the use of oral desmopressin in these indications may not be practical. However, there is currently a recall and temporary halt in production of the nasal spray, so there is perhaps a place for oral administration to substitute for nasal administration, as an alternative user-friendly formulation. Some studies suggest that lower absolute doses of desmopressin in children could still achieve efficacy. A study by Akin (18) demonstrated that a lower dose of desmopressin (0.15 μg subcutaneous) was effective in increasing Factor VIII, VWF:RCo and VWF:Ag levels in children with type 1 VWD, and wider use of desmopressin, especially in developing countries, was recommended. In a retrospective study, half dose desmopressin (0.15 μg/kg IV) was also found to be effective in adult bleeding disorder patients undergoing low to moderate risk invasive procedures (19). There are ongoing studies looking at the feasibility

Table II. Selected V2 receptor locations and functions of V2 agonist at each location.

Therapy area	Organ	V2 agonist function
Bleeding disorders[a], bleeding control[b]	Blood[a]	Factor VIII[a], von Willebrand factor[a]
Renal colic[b]	Ureter[b], Kidney[a]	Antidiuresis[a], other? (such as reduction of intra-ureteral mean pressure[b] or inhibition of smooth muscle fibre contraction[b])
Depression[b], memory[b]	CNS[b]	Cognition[b], memory[b], social behaviour[b], diurnal rhythms[b]
Oncology[b]	Various[b]	Different mechanisms proposed[b]

[a]Actions of desmopressin directly related to established indications. [b]Research reports in areas where desmopressin is not currently indicated for use. CNS, central nervous system; V2, vasopressin receptor 2.

of pharmacokinetic-guided dosing of desmopressin since there is considerable pharmacokinetic variability (20,21). There is also variation in clinical response to desmopressin, which was recently demonstrated to be affected by *VWF* genetic variants (22). These factors suggest that there may be a subset of patients who could benefit from low doses of desmopressin achievable via oral administration, but further studies would be needed in this area.

A systematic review in 2012 noted that desmopressin has been used successfully for prevention of bleeding during pregnancy and postpartum haemorrhage in people with bleeding disorders (23). Most of the studies used 0.3 μg/kg IV infusion (166 cases), while 12 and 20 μg IV desmopressin were used in one case each. Intranasal desmopressin was used in two studies (33 cases) at a dose of 300 μg. Intranasal desmopressin (300 μg for two days) also effectively reduced menstrual blood loss and improved quality of life in patients with abnormal laboratory haemostasis, although the effect of tranexamic acid was greater (24). There may be a role for desmopressin in long-term prophylaxis in patients with vWD, although Factor VIII/von Willebrand factor concentrate is generally the preferred option here (25). It should also be noted that patients with bleeding disorders may develop tolerance to long-term use of desmopressin, and that there are important safety considerations for the long-term use of high-dose desmopressin.

Additional studies-noted during general literature searches-mentioned the use of high dose (0.3-0.4 IV μg/kg in most studies) desmopressin in other bleeding disorders including platelet dysfunction during antiplatelet therapy (26), Hermansky-Pudlak syndrome (27,28), and unclassified bleeding disorders (29,30), but in most cases there was a lack of randomised, controlled trials, and no indication that lower, oral dosing would be effective.

Summary: oral desmopressin in bleeding disorders. An oral formulation of desmopressin would be a more child-friendly formulation for prophylactic use (e.g. before dental surgery) or treatment of bleeding episodes if adequate dosing could be achieved in this patient population. In general, however, bleeding disorders require high doses of desmopressin (0.3 μg/kg IV or 300 μg intranasal) in order for the haematological effects of the drug to be observed. Some studies suggest that half dose (0.15 μg/kg) intravenous desmopressin is still effective, but for oral desmopressin to achieve equivalence, doses would still need to be high.

Desmopressin and bleeding control in patients without a bleeding disorder. In the 1980s, Lawrence Czer's group at the Cedars-Sinai Medical Center in Los Angeles published research indicating that desmopressin reduced bleeding time and improved reoperation rates in patients with mediastinal haemorrhage after cardiopulmonary bypass (31). It was hypothesised that this was due to release of Factor VIII, increase in von Willebrand's factor (an established effect of desmopressin) and improvement in platelet adhesion. Since then, several studies have evaluated desmopressin's potential use in various areas of bleeding control, in patients who do not have a specific bleeding disorder.

A systematic literature review was carried out for studies investigating the use of desmopressin for bleeding control (excluding patients with bleeding disorders-covered in the previous section). Twenty-one studies of interest for which full-text articles were freely available were identified (see supplementary Table SI)-due to an error in the PubMed filtering system, 10 pre-2012 articles were retrieved despite the search string stipulating articles should be from 2012 onwards and these were removed from the final selection. Another five studies were identified through other PubMed searches and citation chasing and were also included in summary Table IV. Studies involved the use of desmopressin for cardiac surgery, endoscopic sinus surgery/rhinoplasty, renal surgery, gastrointestinal surgery and intracerebral haemorrhage.

Cardiac surgery and renal surgery. All except one study of cardiac or renal surgery used the intravenous formulation of desmopressin. Overall, studies in cardiac surgery reported inconsistent findings but generally did not show significant benefit with desmopressin. However, a literature review reported that there are certain subgroups that may benefit from desmopressin use, including patients with demonstrable pre- or perioperative platelet dysfunction as determined by TEG analysis or platelet function assays, those who have received preoperative aspirin within 7 days of surgery, and patients with cardiopulmonary bypass times in excess of 140 min (32). However, further studies are required.

Similar findings were reported in renal surgery (kidney biopsy), with certain subpopulations of patients (serum creatinine ≥1.8 mg/dl and GFR <15 ml/min/1.73 m^2) more likely to experience benefit with desmopressin (33,34).

Endoscopic sinus surgery/rhinoplasty. There were five studies of desmopressin in endoscopic sinus surgery or

Table III. Literature search parameters for PubMed-indexed publications.

Area	Date range	Search string	Inclusion criteria	Exclusion criteria
Bleeding control	1/1/2012-1/9/2022	('Deamino Arginine Vasopressin'[Mesh] OR desmopressin[tw]) AND ('Blood Transfusion'[Mesh] OR 'blood transfusion'[tw] OR 'Epistaxis'[Mesh] OR 'nose bleed*'[tw] OR 'Menorrhagia'[Mesh] OR 'excessive menstrual bleeding'[tw] OR ('tranexamic acid'[Mesh] AND ('2012'[Date-Publication]: '3000'[Date - Publication])) OR 'General Surgery'[Mesh] OR ('surger*'[tw] AND ('2012'[Date - Publication]: '3000'[Date-Publication])) OR ('preop*'[tw] AND ('2012'[Date-Publication]: '3000'[Date-Publication]))) NOT 'bleeding disorder'[tw] NOT 'Blood Coagulation Disorders'[Mesh]	Human patients; vasopressin or desmopressin; English; any type of primary study	Outside scope; case report; MA/SLR; not English language; not about bleeding; not about desmopressin; not human subjects; secondary data
Renal colic	No start date-1/9/2022	('Deamino Arginine Vasopressin'[MeSH Terms] OR 'desmopressin'[Text Word]) AND ('Central Nervous System'[MeSH Terms] OR 'Learning'[MeSH Terms] OR 'Depression'[MeSH Terms] OR 'Electroconvulsive Therapy'[MeSH Terms] OR 'sexual dysfunctions, psychological'[MeSH Terms] OR 'Social Behavior'[MeSH Terms] OR 'Attention Deficit Disorder with Hyperactivity'[MeSH Terms])	Human patients; vasopressin or desmopressin; English; any type of primary study	Animal study; not vasopressin; outside scope; no article available; not English language; not a study; SLR or MA
Central nervous system	No start date-1/9/2022	('Deamino Arginine Vasopressin'[MeSH Terms] OR 'desmopressin'[Text Word]) AND ('Central Nervous System'[MeSH Terms] OR 'Learning'[MeSH Terms] OR 'Depression'[MeSH Terms] OR 'Electroconvulsive Therapy'[MeSH Terms] OR 'sexual dysfunctions, psychological'[MeSH Terms] OR 'Social Behavior'[MeSH Terms] OR 'Attention Deficit Disorder with Hyperactivity'[MeSH Terms])	Human patients; vasopressin or desmopressin; English; cognitive outcome variable; any type of primary study	Animal study; no abstract; not about desmopressin; outside scope; literature review/MA; not English language
Oncology	No start date-1/9/2022	('Deamino Arginine Vasopressin'[Mesh] OR desmopressin[tw]) AND ('Medical Oncology'[Mesh] OR 'oncology'[tw] OR 'Neoplasms'[Mesh] OR 'cancer'[tw] OR 'Breast Neoplasms'[Mesh] OR 'breast cancer'[tw] OR 'Prostatic Neoplasms'[Mesh] OR 'prostate cancer'[tw] OR 'Lung Neoplasms'[Mesh] OR 'lung cancer'[tw] OR 'Colorectal Neoplasms'[Mesh] OR 'colorectal cancer'[tw] OR 'Urinary Bladder Neoplasms'[Mesh])	Human patients; vasopressin or desmopressin; English; any type of primary study	Not human subjects; not vasopressin; outside scope; desmopressin not treating cancer disease; human cell culture; review or MA

MA, meta-analysis; MeSH, Medical Subject Headings; SLR, systematic literature review.

Table IV. Studies of desmopressin in bleeding control.

A, Cardiac surgery

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose	Formulation	(Refs.)
Altun *et a*l, 2017	No benefit	Emergency coronary bypass surgery in patients under the influence of dual antiplatelet therapy: effects of tranexamic acid and desmopressin acetate.	54	dDAVP and control groups had greater duration of closure times, postoperative amounts of drainage, volumes of erythrocyte suspension/plasma, cost of blood products, length of intubation, length of stay in intensive care and time to discharge. dDAVP had no significant effect on bleeding control and delayed haemostatic efficacy of tranexamic acid.	0.3 μg/kg	IV	(115)
Bignami *et al*, 2016	No benefit	Desmopressin after cardiac surgery in bleeding patients. A multicenter randomized trial.	135	No significant difference vs. placebo in terms of number of patients requiring red blood cell transfusion (37/68 vs. 33/67) and no difference in blood loss, mechanical ventilation, intensive care unit stay or mortality.	0.3 μg/kg	IV	(116)
Jahangirifard *et al*, 2017	Benefit	Effect of Desmopressin on the Amount of Bleeding and Transfusion Requirements in Patients Undergoing Heart Transplant Surgery.	48	Mean chest tube drainage at 24 h lower in desmopressin group than the control group. Packed red blood cells less frequently transfused in desmopressin group vs. control group.	0.3 μg/kg	IV	(117)
Jin and Ji, 2015	Unclear or inconsistent benefit	Effect of desmopressin on platelet aggregation and blood loss in patients undergoing valvular heart surgery.	102	Blood loss at 6 h after surgery was reduced in dDAVP group vs. control group. No significant differences in blood loss at 24 h after surgery. Postoperative incidence of fresh frozen plasma transfusion decreased in dDAVP group. There were no differences in red blood cell and platelet transfusion rate between the two groups.	0.3 μg/kg	IV	(118)
Mirmansoori *et al*, 2016	No benefit	The Effect of Desmopressin on the Amount of Bleeding in Patients Undergoing Coronary Artery Bypass Graft Surgery with a Cardiopulmonary Bypass Pump After Taking Anti-Platelet Medicine.	100	IN desmopressin could not reduce the amount of blood loss after coronary artery bypass graft. Desmopressin did not have a significant effect on coagulation status.	40 μg	IN	(119)

Table IV. Continued.

B, Renal surgery

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose	Formulation	(Refs.)
Athavale *et al*, 2019	Unclear or inconsistent benefit	Desmopressin and bleeding risk after percutaneous kidney biopsy.	269	Administration of desmopressin to patients with serum creatinine ≥1.8 mg/dl[a] decreased bleeding risk (P=0.09) but increased bleeding risk when serum creatinine was <1.8 mg/dl (P<0.001). dDAVP should be reserved for patients undergoing percutaneous kidney biopsy who are at high risk for bleeding.	0.3 μg/kg; 30 min prior to biopsy	IV	(34)
Cheong *et al*, 2021	No benefit	No effect of desmopressin administration before kidney biopsy on the risk of major post-biopsy bleeding.	3,018	Blood transfusions more frequent in the desmopressin group; no differences in the incidence of renal artery embolization, blood transfusion and total major bleeding events.	0.3 μg/kg	IV	(120)
Leclerc *et al*, 2020	Unclear or inconsistent benefit	Use of Desmopressin Prior to Kidney Biopsy in Patients With High Bleeding Risk.	413	Despite higher bleeding risk before biopsy, patients using desmopressin had a similar likelihood of symptomatic haematomas and a lower need for urgent radiologic studies compared with those not receiving desmopressin (retrospective cohort study).	0.3 μg/kg	IV	(121)
Radhakrishnan *et al*, 2014	Unclear or inconsistent benefit	Pre-procedure desmopressin acetate to reduce bleeding in renal failure: does it really work?	43	No significant difference was found in bleeding rates between the two groups overall. There was a trend toward benefit in patients with GFR <15 ml/min/1.73 m^{2}[a]	0.3 μg/kg 30-60 min prior to the procedure	IV	(33)

C, Sinus surgery/rhinoplasty

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose	Formulation	(Refs.)
Akbarpour *et al*, 2022	Benefit	Effect of desmopressin on bleeding during endoscopic sinus surgery: A randomized clinical trial.	120	Intranasal desmopressin at a dose of 40 μg 1 h before surgery could reduce bleeding and improve the quality of the surgical field.	20 or 40 μg 60 min prior to anaesthesia	IN	(35)
Haddady-Abianeh *et al*, 2019	Benefit	The Hemostatic Effect of Desmopressin on Bleeding as a Nasal Spray in Open Septorhinoplasty.	30	The Boezaart score, satisfaction scores, bleeding volume and upper eyelid ecchymosis in the group receiving desmopressin were improved compared with those in the control group.	Two puffs of spray in each nostril; 'Minirin with bioavailability of 8 μg'	IN	(36)

Table IV. Continued.

C, Sinus surgery/rhinoplasty

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose	Formulation	(Refs.)
Jahanshahi *et al*, 2019	Benefit	Effect of local desmopressin administration on intraoperative blood loss and quality of the surgical field during functional endoscopic sinus surgery in patients with chronic rhinosinusitis: a triple-blinded clinical trial.	90	Blood loss was lower in the desmopressin group. Surgeons were more satisfied with the surgical field in the desmopressin group than the control group at all registered time points during the surgery procedure (measured at 15, 30, 60 and 90 min).	10 μg in each side of nasal cavity 30 min before the surgery	IN	(37)
Safaeian *et al*, 2021	Benefit	Desmopressin nasal spray reduces blood loss and improves the quality of the surgical field during functional endoscopic sinus surgery.	60	Blood loss in the dDAVP group was lower than that in the placebo group. In more than half of patients on dDAVP, no suctioning was required 1 h after the beginning of surgery, whereas 70% of patients in the placebo group had bleeding scores >1 and thus required suctioning.	A nasal spray of 20 μg	IN	(38)
Shao *et al*, 2015	Benefit	Effect of desmopressin administration on intraoperative blood loss and quality of the surgical field during functional endoscopic sinus surgery: a randomized, clinical trial.	90	Effect of desmopressin on blood loss and quality of the surgical field. Patients in the desmopressin group showed lower requirements for IV reminfentanil and esmolol than controls. Duration of surgery was shorter in the desmopressin group (not significant).	dDAVP 0.3 μg/kg	IV	(39)

D, Gastrointestinal surgery

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose	Formulation	(Refs.)
Wang *et al*, 2020	Benefit	Desmopressin acetate decreases blood loss in patients with massive hemorrhage undergoing gastrointestinal surgery.	48	At 24 h after the surgery, the decrease in haemoglobin in the DDAVP group was lower than that in the normal saline group. Platelet function in the dDAVP group was higher than that in the normal saline group at 24 h.	dDAVP 0.3 μg/kg for 30 min once a day after the surgery	IV	(122)

Table IV. Continued.

E, Intracerebral haemorrhage under antiplatelet treatment							
First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose	Formulation	(Refs.)
Mengel *et al*, 2020	No benefit	Early Administration of Desmopressin and Platelet Transfusion for Reducing Hematoma Expansion in Patients With Acute Anti-platelet Therapy Associated Intracerebral Hemorrhage.	140	No between-group differences in total intracerebral haematoma expansion and intraventricular haematoma expansion were noted.	0.4 μg/kg + platelet transfusion (2 U) within 60 min of intracerebral haemorrhage	IV	(41)

[a]Subpopulations that experienced benefit with dDAVP. dDAVP, desmopressin; GFR, glomerular filtration rate; IN, intranasal; IV, intravenous.

rhinoplasty (35-39)-4 used intranasal desmopressin prior to surgery (20, or 20 and 40 μg), and all found significant benefit with desmopressin, in terms of blood loss and quality of the surgical field. In a randomised trial of low-dose (20 μg) intranasal desmopressin, high-dose (40 μg) intranasal desmopressin and placebo, only the high dose was found to significantly reduce volume of blood loss compared with placebo, as well as doubling the odds of having a good surgical field (35).

Overall, these results suggest that this may be a promising area for future use of the drug at dose levels that could potentially be achieved with oral formulations, although the impact on efficacy of moving from the intranasal formulation to an oral formulation would need to be investigated.

Intracerebral haemorrhage. Neurocritical Care guidelines recommend consideration of desmopressin in antiplatelet-associated intracranial haemorrhage (40). However, the one study in this therapeutic area identified in our search reported no significant benefit with desmopressin (0.4 μg/kg IV) in patients on anti-platelet therapy (41). A recent metanalysis also concluded that the available literature does not support the routine use of desmopressin in the setting of antiplatelet-associated intracerebral haemorrhage (42).

In contrast, a review by Andersen *et al* (26) found that desmopressin improved bleeding time and increased platelet aggregation in patients with intracerebral or subarachnoid haemorrhage while receiving antiplatelet therapy, as well as in non-cardiac surgery patients and in healthy adults and animals exposed to antiplatelet therapy. There were also some observational data to suggest that desmopressin could reduce haematoma expansion in patients with intracerebral haemorrhage or traumatic brain injury. Nevertheless, the authors considered that randomised controlled trials in these areas are still needed.

In terms of oral desmopressin formulations, as the focus of this review, it is likely that oral administration would not only be unsuited to this kind of acute care setting but also would be unable to achieve equivalent dosing to the intravenous formulation.

Summary: oral desmopressin in bleeding control. Most studies of desmopressin in bleeding control identified in this review used the intravenous formulation at high doses that are unlikely to be achieved with oral formulations. In cardiac and renal surgery, results are inconsistent in any case.

However, the use of oral desmopressin as a preventative measure before endoscopic sinus surgery or rhinoplasty may be feasible given that there have been a number of studies reporting significant benefits for bleeding and for the surgical field with intranasal desmopressin. Results cannot necessarily be extrapolated from localised intranasal delivery to oral administration, however, and studies in this area would be needed.

Desmopressin in renal colic. Renal colic is a common urological condition, with a lifetime risk of around 12% in men and 6% in women (43), although estimates vary across studies and geographic regions. It refers to severe pain resulting from the presence of a stone in the urinary system causing acute obstruction, ureteric dilatation, tensile stretch and spasmodic activity (44-46). The ureter releases prostaglandins in response to the obstruction, rendering nociceptors sensitive to stimuli such as bradykinins that induce pain and

other visceral responses such as nausea (47). Prostaglandins also cause increased renal blood flow and down-regulation of the antidiuretic hormone, arginine vasopressin, as well as the contraction of ureteral smooth muscle (47).

In uncomplicated cases of stones up to 10 mm, a conservative approach may be taken, with observation for spontaneous passage for around 4-6 weeks (45). Medical expulsive therapy (MET) is commonly used to increase stone passage rate, decrease time to passage and decrease pain. MET aims to increase ureteral diameter via relaxation of the smooth muscle, and agents including alpha-blockers, calcium channel blockers and prednisolone have been investigated-however, the evidence base for these is limited and some have significant side effects (48-51). MET using alpha-blockers is recommended by the European Association for Urology (EAU) as a potential treatment option for distal ureteral stones >5 mm (51).

Analgesia in renal colic seeks to relax the ureteric smooth muscle and decrease flow within the urinary tract (decreasing the diuretic effect). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis, are first-line therapy recommended by the EAU and are considered superior to opioids (51). However, they are also associated with unwanted side effects such as gastrointestinal bleeding and renal failure (52).

Since the 1990s, a number of reports have been published documenting an analgesic effect of desmopressin, either used alone or in combination with other therapies, in renal colic patients. A nationwide registry study in Denmark confirmed that desmopressin is prescribed in addition to opioids or NSAIDs, and in some cases as monotherapy, to treat renal colic (47).

The mechanism of pain relief with desmopressin has not been comprehensively investigated but is thought to be a result of one or more of the following possible processes (47): reduction in intra-ureteral mean pressure inside the excretory tract, while kidney blood perfusion is maintained; combating the downregulation of AVP that is brought about by prostaglandin release, encouraging antidiuresis via V2 receptors in the kidney; inhibition of smooth muscle fibre contraction (53); release of ß-endorphin from the hypothalamus in response to desmopressin administration leading to central analgesic effects (54), although this has not been proven, and-as discussed in the section of this review on CNS effects-it is unclear whether desmopressin can cross the blood-brain barrier.

Studies of desmopressin in renal colic. Our systematic literature search for studies investigating the use of desmopressin in renal colic identified 13 relevant studies, including 12 interventional studies. Findings are summarised in Table V, with further study details included in supplementary Table SII.

The majority of studies were conducted in Iran (52,55-62). Two studies used the ODT formulation at 60 μg (59) or 60 and 120 μg (63), while all other interventional studies used the intranasal formulation at doses ranging from 20 μg in one study (56) to 40 μg in all others. Some studies investigated desmopressin monotherapy (60-62,64) but most looked at combination therapy.

Overall, mixed findings are reported regarding the efficacy of desmopressin compared with a range of comparators for pain relief in renal colic, although most studies have reported it to have at least some beneficial effects. Moreover, desmopressin has advantages over many of its comparators in terms of ease of administration and tolerability that mean that it could be useful, especially in combination therapy and for ambulatory pain relief. Some studies have noted a variability in response to intranasal desmopressin across patients (65); oral formulations, which have more reliable dosing, may produce more consistent and/or rapid effects. One study has already demonstrated significantly greater pain relief with 120 μg ODT compared with ketorolac (63), and the number of dropouts due to pain escalation was significantly lower in all groups receiving desmopressin (combination therapy or monotherapy at 60/120 μg). It is also of note that several studies only followed patients for a short period (e.g. 30 min) (64,65), although desmopressin may not reach peak effectiveness until one hour after administration with some formulations (52).

A systematic review and meta-analysis published in 2016 found that most studies were low quality but suggested that desmopressin can be used as an adjuvant therapy in renal colic management in combination with opioids (66). Another recent meta-analysis concluded that desmopressin has lower pain reduction properties than comparators (67). However, it should be noted that some patients do not tolerate first-line therapies well, and as such, effective alternatives are needed. We propose that larger, high-quality studies that follow patient response for a sufficient duration would be beneficial in settling the current confusion and inconsistency surrounding the use of desmopressin in renal colic.

Summary: oral desmopressin in renal colic. Oral desmopressin (60-120 μg ODT) may be useful in renal colic but further, high quality studies are needed to confirm the efficacy of desmopressin in this indication. Oral desmopressin could potentially be used as monotherapy (63) or in combination with NSAIDs-the Pricop study showed mild but statistically significant additive analgesic effects after 30 min of follow-up when ketorolac was used in combination with the lower dose of desmopressin (60 μg ODT) (63), suggesting possible supplementary beneficial effects of this drug combination.

Desmopressin and the central nervous system. Vasopressin, and its sister hormone oxytocin (which differs by only two amino acids), are neuropeptides. Both have been implicated in the modulation of social behaviour and the stress response (68-71).

Since the 1970s, there have been a number of sporadic reports suggesting an effect of desmopressin on different functions of the brain or central nervous system (CNS), including memory, learning and attention. It has also been reported that there may be a central mode of action for desmopressin in its established role as an effective treatment for enuresis: an improvement in short-term memory in children with enuresis treated with desmopressin has been reported (72), and pre-pulse inhibition of startle has been found to be impaired in children with enuresis but restored to normal levels by treatment with desmopressin (73). Similarly, benefits of desmopressin treatment on memory function in patients with diabetes insipidus have been reported (74).

Vasopressin receptors in the CNS. There are three vasopressin receptor subtypes: V1a (primarily responsible for

Table V. Comparators and summary of study findings in renal colic.

First author/s, year	Supports dDAVP use?	Comparator	No.	Dose	Summary of findings	(Refs.)
Arhami Dolatabadi *et al*, 2017	No benefit	IV ketorolac	40	40 μg IN	IN desmopressin was less effective than IV ketorolac.	(61)
Kumar *et al*, 2011	No benefit	IM diclofenac	72	40 μg IN	None of the patients on IN desmopressin achieved satisfactory pain relief after 30 min and desmopressin did not enhance the effect of diclofenac.	(64)
Lopes *et al*, 2001	Unclear or inconsistent benefit		61	40 μg IN	IN desmopressin, IM diclofenac and combination therapy equally effective at 10 and 20 min; however, at 30 min, there was a slight increase in pain level with desmopressin monotherapy.	(65)
Masoumi *et al*, 2014	Benefit		120	40 μg IN	Combined IN desmopressin and IM diclofenac was more effective than IM diclofenac alone. Difference started 15 min after drug administration and was maintained at 60 min.	(58)
Roshani *et al*, 2010	Benefit	Diclofenac suppository	150	40 μg IN	Combined IN desmopressin plus diclofenac sodium suppository resulted in prompt pain relief with decreases in pain scores after 15 and 30 min compared with diclofenac monotherapy.	(57)
Jalili *et al*, 2019	No benefit	Indomethacin suppository	124	40 μg IN	No differences in pain reduction between the indomethacin suppository group and the combined IN desmopressin and indomethacin group	(52)
Hazhir *et al*, 2010	Unclear or inconsistent benefit	IM tramadol	90	40 μg IN	IM tramadol or combined IN desmopressin and tramadol showed no significant differences; however, the number of subjects needing supplementary pethidine was lower with desmopressin monotherapy.	(55)
Shirazi *et al*, 2015	Unclear or inconsistent benefit	IM tramadol and indomethacin suppository	120	40 μg IN	Pain decreased in all monotherapy groups (including 40 μg IN desmopressin) but was lowest in those receiving tramadol.	(60)
Kheirollahi *et al*, 2010	Benefit	IM hyoscine N-butylbromide	116	20 μg IN	IM hyoscine N-butylbromide was more effective in combination with IN desmopressin.	(56)
Ghafouri *et al*, 2020	Unclear or inconsistent benefit	IV paracetamol	240	40 μg IN	IN desmopressin had similar efficacy but a faster effect.	(62)
Keshvari Shirvani *et al*, 2015	No benefit	IM morphine	81	60 μg ODT	No benefit in adding desmopressin ODT.	(59)
Pricop *et al*, 2016	Benefit	IM ketorolac	249	120 μg ODT, 60 μg ODT	120 μg desmopressin ODT decreased absolute pain intensity more than ketorolac alone; 60 μg desmopressin and ketorolac in combination was more efficient in decreasing absolute pain intensity than ketorolac monotherapy or desmopressin (60 μg) monotherapy.	(63)

dDAVP, desmopressin; IM, intramuscular; IV, intravenous; IN, intranasal; ODT, orally disintegrating tablet.

vasoconstriction), V1b (primary involved in activation of the hypothalamic-pituitary-adrenal axis) and V2 (primarily responsible for antidiuresis via action in the kidney).

The action of vasopressin in the brain has predominantly been attributed to V1a receptors which are expressed at higher levels in several areas of the brain (75), and have been associated with pair-bonding, aggression and stress management in animal studies (76). V2 receptors are largely excluded from discussions of CNS effects of vasopressin (68,77) because they are considered not to be expressed at high enough levels in the brain. This may limit the relevance of desmopressin, a V2-selective agonist, for effects on the CNS.

However, V2 receptor expression has been reported in human cerebellum (78) and in rat cerebellum (79), as well as in other areas of the developing rat brain (80). The cerebellum is mainly known for its role in motor control/coordination, but may also be involved in other functions including cognition, emotion (81) and working memory (82).

It is also possible that there is some limited residual effect of desmopressin on V1 receptors in the brain-this would require specific investigation, however. It is thought that desmopressin may be able to activate V1b receptors in certain conditions, such as in people with ACTH-dependent Cushing's disease (83)-this interaction may result from upregulation of V1b receptors (or the aberrant expression of type 2 receptors by neoplastic ACTH-producing cells) (84). Some support for the theory that desmopressin may act centrally also comes from case studies of patients with nephrogenic diabetes insipidus and nocturnal enuresis caused by genetic mutations that prevent the kidney being responsive to AVP (and therefore desmopressin). In a number of reports, these patients have nevertheless experienced improvements in their bedwetting, or transition from bedwetting to nocturia, with desmopressin treatment (85,86). It has therefore been proposed that desmopressin may be able to impact enuresis through effects on arousal or other processes, acting via central rather than renal AVP receptors and possibly via V1 rather than V2 receptors.

Can desmopressin reach the CNS? In general, it is thought that desmopressin is unable to cross the blood-brain (or blood-CSF) barrier when administered intravenously (87-89). However, a mechanism of bidirectional saturable transport across the blood-brain barrier for vasopressin has been demonstrated and, from this, it was concluded that a saturable system exists for brain to blood transport of AVP and some structurally similar peptides (90).

One way to bypass the blood-brain barrier is using intranasal administration to deliver drugs to the brain via the olfactory and trigeminal nerve pathways (91). Indeed, intranasal administration of antidiabetic peptides has been demonstrated to allow drug delivery directly to the brain in animals (92) and humans (93), with a view to therapeutic application in Alzheimer's disease (94).

There may be other routes by which desmopressin could exert CNS effects, for example by acting from the periphery to alter gene expression in the brain (95), binding to receptors in the periphery that feed back to the CNS, altering permeability of the blood-brain barrier to other substances (96,97), or by the formation of active fragments that can cross the blood-brain barrier following peripheral administration (98-101). In support of the ability of desmopressin to affect brain function, an inhibitory effect of intravenous desmopressin on hypothalamic dopamine function in humans has been reported (102)-it was unclear whether this was a direct or indirect effect.

Studies of desmopressin in the CNS. A systematic literature search was performed to identify studies that investigated effects of desmopressin on the CNS in humans. Forty-one were identified, and 16 were obtained as full-text articles. Details of these are presented in the comprehensive table in supplementary Table SIII. A small number of additional studies of interest were identified through review of abstracts, citation chasing or more focused literature searches-these are also included in Table VI which provides a brief overview of 23 studies.

All studies had relatively small sample sizes.

Desmopressin was administered intranasally in all studies except two that used intramuscular injection in schizophrenia (103,104). In general, studies with intranasal desmopressin used doses ranging from 20-60 μg/day, although there were some outside this range.

Variable effects of desmopressin on different aspects of CNS function were reported. In Table VI, studies are grouped according to outcome of interest: learning, memory, memory after electro-convulsive therapy (ECT), reaction time, language, cognitive function/affective disorder and schizophrenia. Overall, 14 studies showed a clear benefit of desmopressin for some or all of the chosen endpoints (Table VI), while a further three showed unclear or inconsistent benefit. Memory improvements were seen more often in short-term rather than long-term memory.

Summary: oral desmopressin in the CNS. Further basic research is needed in this area before any conclusions can be drawn regarding effects of desmopressin on the CNS. Although a number of studies suggest effects of desmopressin in areas such as learning, memory or clinical symptoms in certain patient populations, studies are often small and of low quality. Furthermore, there are several outstanding questions regarding the overall concept of using desmopressin to target the CNS. These relate primarily to two major issues: the ability of desmopressin to penetrate the blood-brain barrier or act on the CNS from the periphery, and the localisation of desmopressin-responsive receptors in the brain. Given that studies of CNS effects to date have used the intranasal formulation of desmopressin-a delivery mode which is believed to be able to bypass the blood-brain barrier in certain cases-the extrapolation of findings from these studies to oral desmopressin cannot be made without further studies specifically of oral formulations.

Desmopressin in oncology. Vasopressin receptors are present in some cancer cells, including human lung, breast, pancreatic, colorectal, and gastrointestinal tumours (105). It has been suggested that V1 receptors are associated with cellular proliferation, but that the V2 receptor is associated with anti-proliferative effects (106). Desmopressin, as a selective agonist for the V2 receptor, shows anti-tumour properties in breast, colorectal, lung and prostate cancer models (105).

Mechanisms of action/early results. Stimulation of vascular V2 receptors leads to acute release of haemostatic factors into

Table VI. Summary of selected studies of interest related to desmopressin and the CNS.

A, Learning

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose and formulation	(Refs.)
Anderson *et al*, 1979	Benefit	Passive avoidance learning in Lesch-Nyhan disease: effect of 1-desamino-8-arginine-vasopressin.	3	Ability to learn was repeatedly and consistently improved by dDAVP.	40 'units' IN	(123)
Beckwith et al, 1982	Benefit	Vasopressin analog (DDAVP) facilitates concept learning in human males.	54	The group treated with dDAVP solved all visual discrimination problems faster than the placebo or no treatment control groups; no effect on visual memory.	60 μg IN	(124)
Eisenberg *et al*, 1984	No benefit	The effect of vasopressin treatment on learning in Down's syndrome.	9	Word list learning showed no improvement with drug vs. placebo. Visual verbal paired associated learning task showed trend in favour of active drug.	40 μg/day IN for 10 days	(125)

B, Memory

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose and formulation	(Refs.)
Beckwith *et al*, 1987	Benefit	Vasopressin analogue (DDAVP) facilitates recall of narrative prose.	40	dDAVP associated with improved recall of idea units vs. placebo.	60 μg IN	(126)
Beckwith *et al*, 1995	No benefit	Failure of posttrial administration of vasopressin analogue (DDAVP) to influence memory in healthy, young, male volunteers.	45	dDAVP after the learning trial had no subsequent effect on recall for prose passages 24 h after treatment.	60 μg IN	(127)
Beckwith *et al*, 1990	Unclear or inconsistent benefit	Dose-dependent effects of DDAVP on memory in healthy young adult males: a preliminary study.	70	60 μg dDAVP not significantly different from other doses in terms of free recall but enhanced cued recall when compared with 5 or 15 μg.	60, 30, 15, 5 or 0 μg IN	(128)
Eisenhofer *et al*, 1985	No benefit	No improvement in ethanol-induced memory deficits after administration of a vasopressin analog.	26	No differences between placebo and dDAVP for effects of ethanol on memory scores. Males given dDAVP had, at 3 h after ethanol, more errors for the Benton visual retention test than controls.	50 μg IN	(129)
Guard *et al*, 1986	No benefit	Effects of vasopressin and desmopressin on memory.	40	No significant change in scores between treated groups and controls.	20 μg IN	(130)
Jenkins *et al*, 1982	No benefit	Effect of desmopressin on normal and impaired memory.	18	None of the patients showed significant improvement with dDAVP for any of the test procedures.	40 μg IN four times a day for 2 weeks (1 week in patients with amnesia)	(131)

Table VI. Continued.

B, Memory

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose and formulation	(Refs.)
Millar *et al*, 1987	Benefit	Vasopressin and memory: improvement in normal short-term recall and reduction of alcohol-induced amnesia.	36	40 μg dDAVP could facilitate human short-term memory processes and reduce alcohol-induced amnesia. No benefit for semantic retrieval or reaction time.	40 μg IN	(132)
Müller *et al*, 2001	Benefit	The effect of desmopressin on short-term memory in children with primary nocturnal enuresis.	40	Children with primary nocturnal enuresis treated with desmopressin exhibited improvement of short-term memory.	20 μg IN	(72)
Nebes *et al*, 1984	Benefit	The effect of vasopressin on memory in the healthy elderly.	48	dDAVP reduced response time for short- and long-term episodic memory (but did not affect semantic memory or simple response time).	60 μg IN (10 μg b.i.d. on day 1, 20 μg b.i.d. on day 2 and 30 μg b.i.d. on days 3-8).	(133)
Till and Beckwith, 1985	Unclear or inconsistent benefit	Sentence memory affected by vasopressin analog (DDAVP) in cross-over experiment.	42	dDAVP may facilitate memory, particularly retrieval processes. The effect was clearest for individuals treated with dDAVP during the first test session (vs. placebo). After 1 week, treatment groups showed little or no difference in recall.	60 μg IN	(134)
Weingartner *et al*, 1981	Benefit	Effects of vasopressin on human memory functions.	18	Cognitively unimpaired and impaired adults treated with dDAVP for a period of several days learned information more effectively, as measured by the completeness, organization and consistency (reliability) of recall. dDAVP also appeared to partially reverse the retrograde amnesia that follows electroconvulsive treatment.	30-60 μg IN	(135)

C, Memory following ECT

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose and formulation	(Refs.)
Abdollahian *et al*, 2004	Benefit	Effects of desmopressin (DDAVP) on memory impairment following electroconvulsive therapy (ECT).	50	Increase in memory scores with dDAVP and difference between dDAVP and placebo.	60 μg IN	(136)
Lerer *et al*, 1983	No benefit	Effect of vasopressin on memory following electroconvulsive therapy.	9	No effect of dDAVP.	25 μg IN	(137)

Table VI. Continued.

D, Reaction time/memory

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose and formulation	(Refs.)
Beckwith *et al*, 1983	Unclear or inconsistent benefit	Vasopressin analog influences the performance of males on a reaction time task.	15	dDAVP improved attentional processes in the second but not the first test session using the Sternberg Item Recognition Task, indicating an interaction between dDAVP and prior experience of the task. dDAVP did not influence memory.	60 μg IN	(138)

E, Attention

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose and formulation	(Refs.)
Jennings *et al*, 1986	Benefit	Vasopressin peptide (DDAVP) may narrow the focus of attention in normal elderly.	15	dDAVP increased proportion of attention allocated to primary task.	600 μg/day IN (0.3 mg twice a day)	(139)

F, Language

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose and formulation	(Refs.)
Tsikunov and Belokoskova, 2007	Benefit	Psychophysiological analysis of the influence of vasopressin on speech in patients with post-stroke aphasias.	26	Speech improvement was noted in 88% of cases following administration of dDAVP vs. placebo.	Dose of 0.1 μg IN for 1.5-2 months and total dosage of 4 μg.	(140)

G, Cognitive function/affective disorder

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose and formulation	(Refs.)
Gold *et al*, 1979	Benefit	Effects of 1-desamo-8-D-arginine vasopressin on behaviour and cognition in primary affective. disorder	4	A total of 3 out of 4 patients showed improvement in cognitive function during dDAVP treatment. A total of 2 out of 4 patients also exhibited elevation of mood and amelioration of other affective symptoms.	60-160 mg IN for 3-7 weeks [NB: dosage as described but may be μg]	(141)

Table VI. Continued.

H, Schizophrenia

First author/s, year	Supports dDAVP use?	Title	No.	Results	Dose and formulation	(Refs.)
Brambilla *et al*, 1986	Benefit	Neuropeptide therapies in chronic schizophrenia: TRH and vasopressin administration.	23	Both dDAVP and TRH improved negative symptoms. Memory was improved in 9/13 patients on dDAVP vs. 10/10 patients on TRH.	4 μg every other, day IM	(103)
Brambilla *et al*, 1989	Benefit	Vasopressin (DDAVP) therapy in chronic schizophrenia: effects on negative symptoms and memory.	10	dDAVP induced improvement of negative symptomatology and a trend toward improvement of short- to medium-term memory.	4 μg/day IM	(104)
Hosseini *et al*, 2014	Benefit	Intranasal desmopressin as an adjunct to risperidone for negative symptoms of schizophrenia: a randomized, double-blind, placebo-controlled, clinical trial.	40	dDAVP-treated patients showed significantly greater improvement in the negative symptoms (P=0.001) as well as the PANSS total and general psychopathology subscale scores (P=0.005 and P=0.003; respectively) compared with the placebo group.	20 μg IN	(142)

dDAVP, desmopressin; IM, intramuscular; IN, intranasal; PANSS, positive and negative syndrome scale; TRH, thyrotropin-releasing hormone; ECT, electroconvulsive therapy; b.i.d, twice a day.

the bloodstream, including Factor VIII, tissue-type plasminogen activator and von Willebrand factor (VWF) (107). VWF is involved in several biological processes such as coagulation (as discussed above), vascular normalisation, cancer cell apoptosis and metastatic resistance. Animal models suggest that efficacy of docetaxel in castration-resistant prostate cancer is enhanced when used in combination with desmopressin (108). Phase II trials in humans also show some encouraging results with the use of desmopressin, including a drop in circulating tumour cells in breast cancer patients (109) and a reduction in tumour vascular perfusion in rectal cancer patients with bleeding (110). In animal studies, infusion of desmopressin during surgery appears to inhibit perioperative metastatic events and may impede micro-metastases that occurred before surgery (109,111).

However, high doses of desmopressin have been used in human trials of desmopressin for cancer treatment: two 1 μg/kg intravenous doses (one just before surgery, one 24 h after surgery) in one study (109) and a maximum tolerated dose of 2x0.5 μg/kg/12 h in another (110).

The likelihood of the oral formulations of desmopressin providing adequate dosing for use in oncological treatment is therefore low. As such, we did not perform an extensive review of the literature on this topic, and intend to carry out a comprehensive review of the use of desmopressin (all formulations) in this therapeutic area as a separate exercise.

4. Conclusion

The use of desmopressin has been explored in a multitude of diverse areas since it was first synthesised (1). Since many of these have not been formally investigated for the purpose of regulatory approval, further studies and RCTs will be needed before any new indications can be recommended. Renal colic is perhaps one of the most promising areas with viable mechanism(s) of action and a reasonably supportive literature on desmopressin use. More studies are required to confirm benefits with oral formulations of desmopressin at standard doses, in monotherapy or combination therapy. Doses at the higher end of the normal range have yielded the most promising results, but dose-finding studies are needed, and the ideal protocol and management of up-titration are yet to be determined.

In bleeding control, most studies of desmopressin that were identified used the intravenous formulation at high doses that are unlikely to be achieved with oral formulations. In cardiac and renal surgery, results are inconsistent but the use of oral desmopressin as a preventative measure before endoscopic sinus surgery or rhinoplasty may be feasible-however, the relevance of intranasal vs oral administration must be investigated. Desmopressin has established efficacy in bleeding disorders but high doses (0.15-0.3 μg/kg IV) are required. Achieving this level of dosing with oral formulations would be challenging.

Further basic research is needed in the CNS (e.g. location of desmopressin-responsive receptors, relevance of blood-brain barrier) before viable uses for oral desmopressin can be properly explored.

Desmopressin has demonstrated intriguing anti-cancer effects in a number of studies, many of which are animal/preclinical. In the small number of human trials, however, high doses of desmopressin have been used (0.5-1 μg/kg IV), again meaning that use of oral formulations is unlikely to be practical.

There are other areas of research that are in their infancy, that may yet prove to be important avenues of investigation for oral forms of desmopressin, such as the bladder and bladder contractility (112), patients with spinal cord injury, and older adults with renal impairment. These are not discussed in this manuscript as there are not yet sufficient studies to gauge the potential role of desmopressin. However, the very fact that we are continuing to learn about credible uses of a drug that was first developed over 50 years ago is testament to the complexity of the human body and the untold possibilities of established, as well as novel, medicines.

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Authors' contributions

KE, THL, GBK, SR, JPW, JVW, AEK, LD, FH, AFS, JPN and KVJ conceived and designed the study. THL performed the literature searches. KE, THL, KVJ and JPN interpreted the data and drafted the manuscript. Data authentication is not applicable. All authors critically reviewed the manuscript, and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

KE has received grants and honoraria to his institution from Ferring, Medtronic, Astellas and Idorsia. THL has worked as a consultant for Ferring Pharmaceuticals. JVW has participated in advisory boards and safety boards and has received speaker fees from Alexion, Ferring, Astellas and Alnylam. FH has received speaker fees from Astellas. JPN is a former full-time employee of Ferring Pharmaceuticals. KVJ is a full-time employee of Ferring Pharmaceuticals. The other authors declare that they have no competing interests.

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