SYSTEMATIC REVIEW

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Evidence for the use of demeclocycline in the treatment of hyponatraemia secondary to SIADH: a systematic review

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SUMMARY

Aims: Hyponatraemia (HN) is the most common electrolyte balance disorder in clinical practice. Since the 1970s, demeclocycline has been used in some countries to treat chronic HN secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH). The precise mechanism of action of demeclocycline is unclear, but has been linked to the induction of nephrogenic diabetes insipidus. Furthermore, the safety profile of demeclocycline is variable with an inconsistent time to onset, and a potential for complications. There has been no systematic evaluation of the use of demeclocycline for the treatment of HN secondary to SIADH to date. A systematic literature review was performed to obtain an insight into the clinical safety and efficacy of demeclocycline for this condition. **Methods:** Embase™, MEDLINE®, MEDLINE® In-Process, and The Cochrane Library were searched on two occasions using MeSH terms combined with free-text terms. References were screened by two independent reviewers. Relevant publications were then extracted by two independent reviewers, with a third reviewer collating and finalising extractions. **Results:** The searches returned a total of 705 hits. 632 abstracts were screened after the removal of duplicates. Following screening, 35 full-length publications were reviewed. Of these, 17 were excluded, resulting in 18 studies deemed relevant for data extraction. Two were randomised controlled trials (RCTs), 16 were non-RCTs, and 10 were case reports. **Discussion:** Although most reports suggest that demeclocycline can address serum sodium levels in specific patients with HN, efficacy is variable, and may depend upon the underlying aetiology. Demeclocycline dose adjustments can be complex, and as its use in clinical practice is not well defined, it can differ between healthcare professionals. **Conclusion:** There is a lack of clinical and economic evidence supporting the use of demeclocycline for HN secondary to SIADH. Patients receiving demeclocycline for HN secondary to SIADH must be closely monitored.

Review criteria
Embase™, MEDLINE, MEDLINE In-Process, and The Cochrane Library were searched on two occasions using relevant MeSH terms combined with free-text terms. References were screened by two independent reviewers. Relevant publications were then extracted by two independent reviewers, with a third reviewer collating and finalising extractions.

Message for the clinic
There is a lack of high-quality clinical evidence supporting the therapeutic use of demeclocycline for HN secondary to SIADH. The safety profile of demeclocycline is variable with an inconsistent time to onset, and a potential for complications. Economic evaluations or HRQoL studies of demeclocycline for the treatment of HN secondary to SIADH have not been performed. Patients receiving demeclocycline must be closely monitored.

Introduction

Hyponatraemia (HN), defined as a serum sodium concentration < 135 mmol/l, is the most common metabolic disorder of body water and total body sodium concentration. HN is usually associated with a disturbance in vasopressin [antidiuretic hormone (ADH)], which can be synthesised independently of serum osmolality or circulating fluid volume under specific pathological or pharmacological conditions (1). Clinical criteria for the syndrome of inappropriate antidiuretic hormone secretion (SIADH) were established by Bartter and Schwartz (2) and have remained largely unchanged ever since (1). SIADH accounts for one-third of all cases of HN (3).

Hyponatraemia occurs in approximately 30% of hospitalised patients (1,4) and is a clinical feature in 15–20% of emergency admissions (1). HN has a wide range of aetiologies across several patient populations. In the great majority of patients, its aetiology is multifactorial (5). HN secondary to SIADH is associated with significant morbidity (6), mortality (7–10) and increased length of hospital stay (11). Symptoms are associated primarily with the severity of the HN, and range from confusion and vomiting in mild HN (< 135 mmol/l sodium) to seizures, coma and death

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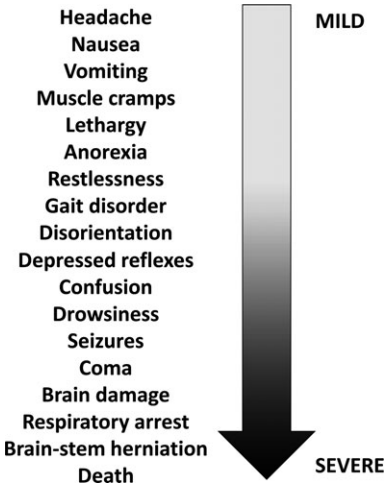

Figure 1 Morbidity and symptoms associated with hyponatraemia (4,13)

in severe cases (< 125 mmol/l sodium; Figure 1) (4,12,13). In addition to symptoms, patients are subject to serious sequelae of HN, including gait abnormalities, falls (14), and an increased fracture risk (15). Such morbidities are clinically significant, as HN is particularly common in elderly people (12).

There is a substantial economic healthcare burden associated with HN, which include significant increases in length of hospital stay, hospital costs and intensive care unit (ICU) costs, as well as an increase in the risk of ICU admission and 30-day hospital readmission. Studies in the USA estimate that direct costs for treating HN range from $1.6 to $3.6 billion annually (16).

Current management strategies for acute symptomatic HN secondary to SIADH comprise hypertonic (3%) saline given either via bolus or continuous intravenous infusion, with or without diuretics. Patients with euvolaemic hypo-osmolality because of SIADH do not respond to isotonic saline, and occasionally, this causes HN to worsen (16). In chronic HN (< 135 mmol/l for > 48 h) secondary to SIADH, fluid restriction is considered first-line treatment in patients without severe symptoms or where hypovolaemia is not suspected (1,16). Fluid restriction between 500 and 1000 ml/day is recommended, according to HN severity (17). Pharmacological therapy generally comprises a vaptan (specific vasopressin-2 receptor antagonists) or demeclocycline in some countries (e.g. France and the UK); other options may include urea or loop diuretics or combinations of above treatments (16).

The aim of HN management was to normalise the serum sodium concentration whilst avoiding the risk of osmotic demyelination syndrome (ODS; previously known as central pontine myelinolysis). It is important to limit the correction of sodium to a maximum rate of 12 mmol/24 h, and to this end, it is important that patients are in an environment suitable for monitoring with regular estimations of sodium levels. If HN is known to be of short duration (< 48 h), correction may be carried out at a faster rate as the risk of cerebral oedema in a patient with severely symptomatic HN outweigh the risks of ODS. It should also be remembered that often, the aim was to restore the sodium to a 'safe' level rather than achieve sodium normalisation. Most physicians suggest regular review of sodium levels and less invasive action once sodium levels reach 120–125 mmol/l (16).

Demeclocycline is a tetracycline derivative antibiotic, with a marketing authorisation in the UK for the treatment of chronic HN associated with SIADH secondary to malignant disease, where water restriction is ineffective and the patient does not have concomitant cirrhosis (18). In France, demeclocycline is reimbursed for the treatment of SIADH, particularly with an origin of paraneoplastic syndrome with chronic hyponatraemia (< 125 mmol/l) associated with inappropriate natriuresis, and/or clinical signs associated with hyponatraemia resistant to fluid restriction (19). Although its mode of action has not yet been established, it is thought that demeclocycline induces nephrogenic diabetes insipidus in approximately 60% of patients with HN secondary to SIADH, resulting in decreased urine concentration and rebalancing of body sodium concentrations (12,16). Onset of action is unpredictable, usually occurring after 2–5 days, but occasionally taking longer (3,12,16).

Treatment with demeclocycline has been associated with gastrointestinal intolerance, including nausea and vomiting, nephrotoxicity and renal failure (18); cases of reversible renal failure have also been reported (20–22). As with all antibiotics, overgrowth of resistant organisms may cause candidiasis (18).

To our knowledge, there has been no systematic evaluation of the use of demeclocycline for the treatment of HN secondary to SIADH to date, and its use appears to be supported by subjective familiarity rather than objective evidence. Therefore, a systematic literature review of all available evidence was performed to obtain an insight into the clinical safety and efficacy of demeclocycline for this condition. To further understand the financial impact of treating with demeclocycline, an economic component was included within the search criteria.

Methods

A comprehensive search strategy was employed following Preferred Reporting Items for Systematic

reviews and Meta-Analyses (PRISMA) standards (23). Embase™, MEDLINE®, MEDLINE® In-Process, and The Cochrane Library were searched using Medical Subject Heading (MeSH) terms, combined with free-text terms (see Appendix A for full search strings). Disease search terms comprised terminological variations of SIADH, HN and key clinical indicators (e.g. sodium serum and urine osmolality). References were then limited to those relating to demeclocycline, and considered relevant if primary data sources examined the use of demeclocycline in patients with HN because of SIADH.

Inclusion criteria for the search output were limited to any study examining the clinical efficacy or long-term/real-world effectiveness of demeclocycline, case reports with more than five patients where only clinical efficacy (rather than safety) was reported, or case reports with one or more patients reporting any safety outcomes. In addition, studies presenting cost-effectiveness or health-related quality of life (HRQoL) data for demeclocycline in the treatment of HN associated with SIADH were also included.

Potentially relevant references identified from the search output were screened electronically by two independent reviewers and any differences subsequently adjudicated by a third reviewer. Full publications of the resulting, potentially relevant studies were then reviewed before the included study list was finalised. Relevant publications were extracted into a predesigned data extraction table by two independent reviewers, with a third reviewer collating and finalising the extractions. Papers published in languages other than English or French were included only if sufficient data were available in English-language abstracts. Quality assessment was conducted for randomised controlled trials (RCTs) and cohort studies using the 2011 Scottish Intercollegiate Guidelines Network checklists (www.sign.ac.uk).

The comprehensive literature search was performed on 28 May 2014. Subsequently, a second search was undertaken to identify relevant studies published between March and December 2014; searches occurred on the 9 December 2014 and were performed to an identical protocol.

Results

Search outputs

Searches outputs from the initial protocol (28 May 2014) returned 679 hits. After the electronic removal of 71 duplicate references, 608 abstracts were screened. Upon completion of dual electronic screening, the full-length publications of 25 studies were ordered for full review; five further studies were available as conference abstracts only. Of these, 12 were excluded (Appendix B summarises the excluded papers), resulting in 18 studies deemed relevant for data extraction.

Results from the second, updated literature search (March to December 2014) produced 26 hits. After the removal of two duplicate references, 24 abstracts were screened; five studies were identified for full review following electronic screening. Of these, all abstracts were excluded (Appendix B), resulting in no additional studies deemed relevant for data extraction (Figure 2).

Systematic review

Of the 18 studies deemed relevant for data extraction, two RCTs were identified (Table 1) (24). Alexander et al. compared demeclocycline with placebo in nine patients with chronic psychiatric illness and episodic or chronic HN (< 135 mmol/l) associated with polydipsia (24); Horattas et al. compared demeclocycline with placebo in 30 patients undergoing elective coronary artery bypass grafting (CABG) (25).

In total, 16 non-RCTs were considered relevant, comprising six cohort studies (four observational studies (20,22,26,27), two retrospective chart analyses (21,28), and 10 case reports (29–38) (Tables 2 and 3, respectively); no cost-effectiveness or HRQoL studies were identified. Quality assessments for all studies other than case reports are presented (Appendix C).

RCT evidence for the effectiveness and safety of demeclocycline

A comparison of demeclocycline with placebo in nine patients with chronic psychiatric illness suggested, there are no significant differences in mean serum sodium concentration after 3 weeks' treatment (131.4 mmol/l and 134.1 mmol/l, respectively). There were no significant differences between treatments in the frequency of episodes of serum sodium levels < 125 mmol/l ($p = 0.78$). All patients experienced episodes of HN during the study; no adverse events related to demeclocycline were reported (24).

Horattas et al. reported a prospective, double-blind, placebo-controlled study of 30 patients undergoing elective CABG. Patients were randomised to receive either placebo or demeclocycline 1200 mg/day at pre-operative Day 5 and continuing through to postoperative Day 2. Following placebo, serum sodium concentration was significantly reduced from pre-operative levels while serum sodium and osmolality was within normal range in the demeclocycline group ($p < 0.01$); urine osmolality increased significantly with placebo on postoperative Day 1 ($p = 0.04$). At postoperative Day 2, serum sodium concentrations in the placebo group continued at a

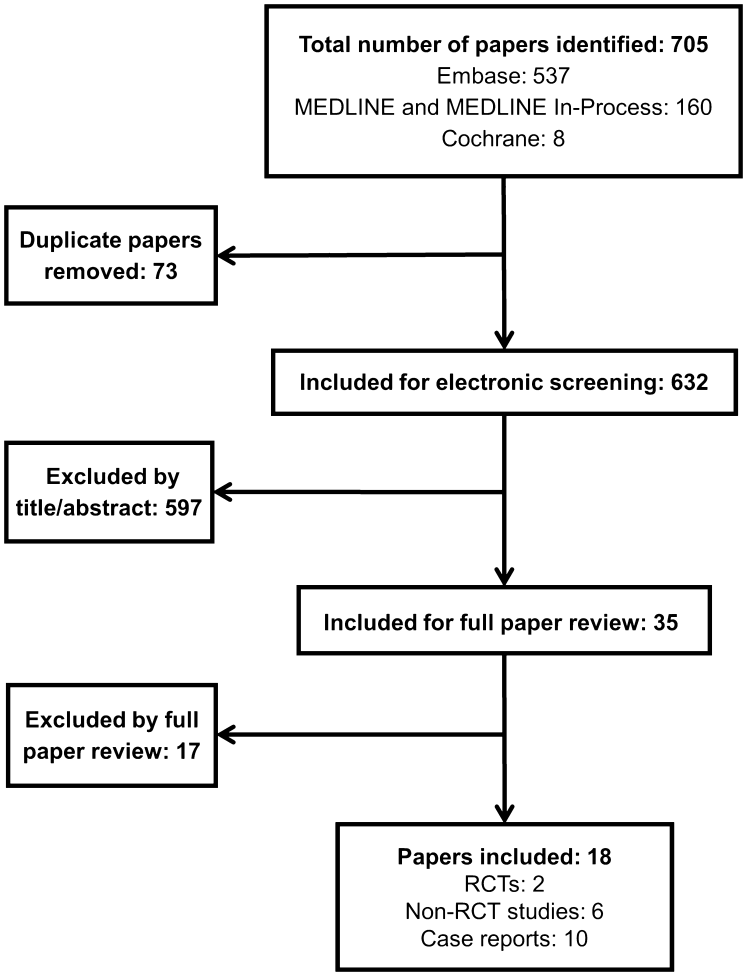

Figure 2 Combined PRISMA flow diagram for the original systematic review and update, showing the total combined publications detected in the original and updated literature searches. As there was a 3-month overlap between search dates, some publications may be detected twice. An adjustment for this possibility was not made. RCT, randomised controlled trial

reduced level compared with baseline, but not with demeclocycline (25). Two patients discontinued demeclocycline owing to skin hypersensitivity and gastrointestinal upset, and four reported mild gastrointestinal upset (25). RCT data for the effectiveness and safety of demeclocycline are presented in Table 4.

Non-randomised cohort studies of demeclocycline

Four observational cohort studies were identified and reported a total of 39 patients with HN secondary to SIADH. All four studies reported an increase in mean serum sodium levels during treatment with demeclocycline at doses of up to 1200 mg/day (20,22,26,27).

Two studies reported adverse events associated with demeclocycline, including azotemia (nine patients in total; two discontinued demeclocycline), renal function impairment (two patients) and nausea (one patient) (20,22). Demeclocycline effectiveness and safety data reported in observational cohort studies are presented in Table 5. Two retrospective chart analyses reported the impact of demeclocycline in a further 21 patients (21,28).

Brewerton et al. reported on six psychiatric patients with a history of carbamazepine responsiveness who developed clinically significant carbamazepine-induced HN. Treatment with demeclocycline was associated with significant increases in serum sodium levels in five patients compared with pretreatment concentrations (increases from 130.1 to 136.7 mmol/l). Safety data were not reported in this study (28).

A retrospective review of 15 patients with malignancies treated with demeclocycline for serious HN, without a specific diagnosis of SIADH, reported an increase in mean serum sodium. From pretreatment

Table 1 Included randomised controlled trials – study design

Author, year [study name]	Patient population	Study design	Eligibility criteria	Interventions	Study outcomes	Demeclocycline dose
Alexander et al. 1991 (24)	Nine psychiatric patients (six male), aged 31–47 years (mean, 38.3 years), with polydipsia-HN	Randomised, double-blind, placebo-controlled cross-over trial	Chronic psychiatric illness and documented episodic or chronic HN (< 135 mmol/l) associated with polydipsia	Demeclocycline or placebo Stable daily doses of neuroleptics	Body weight; serum sodium levels; number of episodes of sodium levels <125 or < 135 mmol/l	300 mg for 3 weeks (twice daily for 7 days; three times daily for 7 days; four time daily for 7 days)
Horattas et al. 1998 (25)	Thirty patients (20 male), aged 40–70 years (mean, 61.4 years), undergoing elective coronary artery bypass grafting	Randomised, double-blind, placebo-controlled clinical study	Normal electrolytes and renal function Exclusions: renal or hepatic dysfunction; endocrine abnormalities; pregnancy; recent antibiotic use; hypersensitivity to tetracycline	600 mg DMC or placebo twice daily, beginning 5 days pre-operatively and continuing through postoperative day 2 Pain medication and/or antihypertensives	Serum electrolytes; complete blood counts; prothrombin time; partial thromboplastin time; arterial blood gases; urine electrolytes; osmolality; serum vasopressin	600 mg (twice daily) from day 5 pre-operation to day 2 post operation

DMC, demeclocycline; HN, hyponatraemia.

values of 119 mmol/l, sodium levels were raised to a mean peak of 139 mmol/l after 3–28 days (21).

In total, 80% of patients ($n = 12$) developed azotemia and three died within 10 days of receiving demeclocycline. Although the deaths were because of advanced infections and malignancy, three presented with marked azotemia; the renal dysfunction associated with demeclocycline was considered as a possible contributor to the deaths. Of the six patients with severe azotemia (serum urea nitrogen > 25 mg/dl), five patients were receiving concomitant nephrotoxic or antianabolic agents: aminoglycoside antibiotics, amphotericin B and corticosteroid (21).

Case reports involving demeclocycline

Ten case reports, detailing 11 patients in total, presented safety data pertaining to demeclocycline (29–38). Demeclocycline effectiveness and safety data reported in case studies are presented in Table 6.

Three reports associated deterioration in renal function with demeclocycline in four patients with a diagnosis of SIADH (30,31,35). Distinct but reversible episodes of glomerular filtration rate (GFR) reduction were observed in two patients (31), with acute renal failure reported in a third receiving demeclocycline at up to 2400 mg/day (35). A fourth patient (94-year-old male hospitalised following collapse and subsequent diagnosis of SIADH) died of irreversible acute renal failure that authors attributed to dehydration associated with demeclocycline 1200 mg/day and a compromised fluid intake (30).

Two case reports described the development of hyperphosphaturia during demeclocycline treatment for HN secondary to SIADH. Upon follow-up, both patients presented with malignancies considered related to elevated phosphate levels, which recovered following discontinuation of demeclocycline. Authors of both reports considered the phosphate diabetes related to selective demeclocycline-induced renal toxicity (29,32).

A further two reports describe severe gastric intolerance leading to discontinuation of demeclocycline (33,34). In one case, a 76-year-old male admitted with grand mal seizures and a previous history of peptic ulcer, severe gastric intolerance occurred after a single dose of demeclocycline (33).

A single case study of a 61-year-old male with SIADH reported normalisation of serum sodium levels with demeclocycline (600 mg/day). After a month, demeclocycline was discontinued but followed by a rapid fall in both osmolality and level of consciousness. Reinstitution of treatment led to biochemical and clinical improvement; the patient was discharged on demeclocycline 3 months after admission (36).

A Japanese report of a 63-year-old female with SIADH treated by strict water restriction, and administration of sodium, dexamethasone and demeclocycline, highlights correction of serum sodium from 93 to 137 mmol/l within 3 days of treatment.

Table 2 Included cohort studies – study design

Author, year	Patient population	Study design	Eligibility criteria	Interventions	Study outcomes	Demeclocycline dose
De Troyer et al. 1977 (20)	Seven male patients with lung carcinoma, aged 48–76 years	Observational study	SIADH	DMC	Serum sodium; urine osmolality; blood urea, creatinine; water clearance	300 mg DMC four times daily, reduced to 600 mg/day after 10 days.
Forrest et al. 1978 (26)	Ten patients (eight male) with chronic SIADH, aged 6–68 years	Observational study	HN despite fluid restriction; SIADH	DMC Three patients given lithium prior to DMC.	Serum sodium; urine osmolality; urinary sodium excretion	600–1200 mg DMC daily given to 10 patients.
Goldman and Luchins, 1985 (27)	Eight psychiatric patients (seven male), aged 43–54 years, with polydipsia-HN	Observational study	Compulsive water drinkers; hyponatraemic (115–130 mmol/l); not taking carbamazepine	DMC Stable daily doses of neuroleptics	Serum sodium; urine osmolality	600 mg (twice daily) for 3 weeks
Perks et al. 1979 (22)	Fourteen patients (seven male); mean age of 61 years.	Observational study	Diagnosis of SIADH based on De Troyer and Demanet (1976) criteria (37)	DMC	Serum electrolytes, urea, creatinine, osmolarity and packed cell volume	1200 mg/day
Brewerton and Jackson, 1994 (28)	Six psychiatric patients (one male), aged 37–80 years (mean 56.0 years)	Retrospective chart analysis	Patients taking carbamazepine who were forced to discontinue because of HN not associated with psychogenic polydipsia	DMC Carbamazepine was administered concomitantly or initiated 3–7 days after DMC	Mean serum sodium	300 mg (twice daily), increased to 600 mg (twice daily) by day 3–5 Average duration of treatment was 11.3 days
Trump, 1981 (21)	Patients with malignancies who received DMC for 4 or more days for serious HN (n = 15)	Retrospective review of patient records	Serious HN (< 125 mmol/l); no oedema or dehydration; normal serum creatinine and urea nitrogen	DMC Seven patients were additionally receiving corticosteroids	Serum sodium, osmolality, urea nitrogen; urine sodium, osmolality; average daily intake/output; bilirubin, weight	600–1200 mg/day

DMC, demeclocycline; HN, hyponatraemia; SIADH, symptom of inappropriate antidiuretic hormone secretion.

Subsequently, the patient became comatose and developed quadriplegia. After 12 months of hospitalisation, the patient died of septic shock. Computed tomography scans and brain stem auditory responses were indicative of ODS (38). Data for this case study were obtained from the English language abstract and figures presented within the report.

A final study reported seizures and altered mental state in a 78-year-old female patient with a history of hypothyroidism, rheumatoid arthritis and early Alzheimer's disease admitted for severe HN, which was considered secondary to SIADH. The patient was treated with demeclocycline (900 mg/day) and discharged under fluid restriction. After 6 weeks, she was readmitted; laboratory investigation identified severe hypernatraemia (serum sodium, 185 mmol/l) resulting from over-correction of HN. The authors recommended that demeclocycline should be reserved for patients for whom strict fluid restriction is unsuitable (39).

Discussion

Hyponatraemia can lead to a wide spectrum of clinical symptoms and presents in a range of conditions. Despite this, the diagnosis and management of patients remains problematic (1,3), particularly because of the heterogeneous nature of HN (40). In addition, treatment guidance has been generally oversimplistic, without clear consensus, and not reflective of the range of clinical issues encountered in current daily practice (1).

The literature search and review demonstrates a paucity of available high-quality data for the effectiveness and safety of demeclocycline in the treatment of HN secondary to SIADH; no relevant economic

Table 3 Relevant case reports – study summary

Author, year	Patient population	Interventions	Outcome	Author conclusion
Antonelli et al. 1993 (29)	A 59-year-old man Slight fever, dyspnoea, weight loss, asthenia and mental slowness	300 mg DMC twice daily for about 3 weeks Water restriction Hypertonic saline iv Corticosteroid treatment for 10 months	Patient developed phosphate diabetes after 4 days of DMC Progressive amelioration of the symptomatology and resolution of SIADH after DMC discontinuation and the start of corticosteroids	Phosphate diabetes may be related to selective DMC-induced tubulopathy
Curtis et al. 2002 (30)	A 94-year-old man hospitalised following collapse Diagnosis of SIADH	300 mg DMC three times daily plus fluid restriction Nine days after admission, DMC increased to four times daily Metronizadole Benzydamine hydrochloride mouth washes	Fatal acute renal failure	Short-term DMC can effectively control symptomatic HN but caution is required because of its potential nephrotoxicity Authors note a danger of dehydration in patients whose fluid intake has become compromised Authors suggest that had DMC been discontinued once the HN had resolved, the development of acute renal failure would have been avoided
Danovitch et al. 1978 (31)	Two patients: 1. A 51-year-old man with oat-cell carcinoma of the lung. Diagnosis of SIADH 2. A 60-year-old-man with 4-week history of confusion and drowsiness. Diagnosis of SIADH	1. 1200 mg DMC daily plus cyclophosphamide 2. 1200 mg DMC daily	DMC treatment corrected HN and hypo-osmolality, but was discontinued in both patients owing to deterioration of renal function	Potentially dangerous side effects exclude routine use of DMC Overall, DMC is effective in the treatment of SIADH, but has a potential to lead to a deterioration of renal function
Decaux et al. 1981 (33)	A 76-year-old man admitted to hospital because of grand mal seizures SIADH diagnosed	A single dose of DMC Water restriction Urea infusion iv Furosemide	Patient had severe gastric intolerance to DMC and the drug was stopped after the first dose	HN was controlled with furosemide after intolerance to DMC
Decaux et al. 1985 (32)	A 62-year-old woman Heavy smoker reporting weakness and memory loss Diagnosis of SIADH Oat-cell carcinoma	300 mg DMC twice daily	DMC corrected HN but led to phosphate diabetes	Phosphate diabetes appeared after therapy with DMC and persisted for 3 months The augmentation in phosphate clearance was unrelated to serum sodium levels Phosphate diabetes was related to selective DMC-induced renal toxicity
Heim et al. 1977 (34)	75-year-old woman, decline in general condition and pleural effusion (Two further cases not receiving DMC are reported)	DMC 1200 mg/day	HN was corrected by fluid restriction; addition of DMC resulted in increased fluid clearance, but the patient developed vomiting and diarrhoea on day 4 and DMC was stopped on day 7	DMC is a relatively non-toxic antibiotic which was shown to be effective; however, treatment was interrupted on day 8 owing to vomiting and diarrhoea The dose of 1200 mg/day may have been too strong for this patient
Padfield et al. 1978 (35)	A 64-year-old man with SIADH following head injury and meningitis	300 mg DMC four times daily followed by 600 mg DMC four times daily Fixed fluid intake	600 mg DMC four times daily rapidly corrected all biochemical features of SIADH Acute renal failure was possibly induced by DMC On discontinuation of DMC normal renal function returned.	DMC corrected the biochemical abnormalities of SIADH Possible evidence of nephrotoxicity

Table 3 Continued

Author, year	Patient population	Interventions	Outcome	Author conclusion
Perks et al. 1976 (36)	A 61-year-old man with memory deficit Inoperable carcinoma diagnosed 7 months after original admission	600 mg DMC daily Fluid restriction	Treatment with DMC led to clinical and biochemical improvement	DMC is a safe and effective treatment that in this case allowed discharge from hospital This regimen may simplify outpatient management of other patients with this syndrome
Shimoda et al. 1986 (note, published in Japanese) (38)	A 63-year-old woman hospitalised after losing consciousness; prior surgery for ruptured anterior artery Diagnosis of SIADH	900 mg/day DMC 16 mg/day dexamethasone	Patient became comatose and developed quadriplegia after rapid correction of serum sodium levels Patient died of septic shock after 12 months of hospitalisation	Computed tomography scans and brain stem auditory responses were indicative of ODS
Soudan and Qunibi, 2012 (39)	A 78-year-old woman with history of hypothyroidism, vitiligo, rheumatoid arthritis and early Alzheimer's dementia Hospitalised with severe HN diagnosed as secondary to SIADH.	300 mg DMC three times daily. Fluid restriction Normal saline infusion Furosemide Existing medication: Methotrexate Memantine HCL Mirtazapine Sulfamethoxazole and trimethoprim	Patient developed severe HN as a result of rigid fluid restriction and DMC therapy Serum sodium levels stabilised after discontinuation of DMC	DMC should be reserved for patients unable tolerate or unwilling to follow strict fluid restriction

DMC, demeclocycline; HN, hypernatraemia; iv, intravenous; ODS, osmotic demyelination syndrome; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

evaluations or HRQoL studies were identified. With the exception of case reports, no published studies have addressed the use of demeclocycline for SIADH-associated HN for more than 15 years (20,22,24–27). Despite its long history in the treatment of HN secondary to SIADH, the use of demeclocycline is largely based on clinical experience rather than objective evidence. Although a lack of robust evidence from RCTs is by no means uncommon in medicine, a systematic appraisal of all published studies and case reports was necessary to appraise the efficacy and safety of demeclocycline treatment.

Examining the studies that are available, only two compared demeclocycline with placebo (24,25). Of these RCTs, one did not demonstrate any significant differences in mean serum sodium levels after 3-weeks' treatment. However, this study enrolled patients with psychosis and episodic or chronic polydipsia-associated HN (mean duration of 5.4 years) who did not have a specific diagnosis of SIADH (24). In addition, the dosing ranges of demeclocycline were initially relatively low (escalating from 600 mg/day to 1200 mg/day by week 3), compared with the recommended initial dose of 900–1200 mg/day (18). The second RCT identified also included patients without a diagnosis of SIADH, but concluded that demeclocycline prevented HN because of increased secretion of ADH, commonly seen in patients undergoing CABG procedures (25).

The mode of action of demeclocycline on ADH-induced water flow is not well understood, but the mechanism of therapeutic effect involves induction of nephrogenic diabetes insipidus (12,41). While no studies have systematically evaluated the side effects associated with demeclocycline, several studies have identified safety issues associated with the onset of nephrogenic diabetes insipidus, particularly renal dysfunction (20–22,30,31,35). In some patients, polyuria can be profound and patients can become markedly symptomatic, occasionally developing hypernatraemia if access to water is severely restricted (12,39). Patients with known liver disease should not receive more than 1 g/day demeclocycline (18). In addition, monitoring of both renal and hepatic function should be performed regularly (18,42).

Onset of action for demeclocycline is unpredictable and reported to range from 2 to 5 days, complicating dose adjustments (12,16). Two reports describe severe gastric intolerance leading to treatment discontinuation (33,34); one incident occurred following a single dose of demeclocycline in a 76-year-old male with grand mal seizures and SIADH.

Table 4 Efficacy and safety results – randomised controlled trial summary

Author, year	Serum sodium (pretreatment)	Serum sodium (post treatment)	Urine sodium (pretreatment)	Urine sodium (post treatment)	AEs (total)	AEs (individual)	SAEs (total)	Author conclusion	Comments
Alexander et al. 1991 (24)	On placebo: Mean of 131.4 mmol/l in third week Episodes of serum sodium <125 mmol/l, 13 of 110 measurements	On DMC: Mean of 134.1 mmol/l in third week Episodes of serum sodium <125 mmol/l, 10 of 103 measurements	NR	NR	0	0	0	No significant effect of DMC on serum sodium of in psychotic patients with polydipsia-HN.	Patients not explicitly diagnosed with SIADH
Horattas et al. 1998 (25)	Pre-operative: DMC mean: 138.9 mmol/l Placebo mean: 138.1 mmol/l	Postoperative day 2: DMC mean: 138 mmol/l approx. Placebo mean: 135.5 mmol/l approx.	NR	NR	Two patients discontinued	Hypersensitivity (rash) leading to discontinuation: 1/30 GI upset leading to discontinuation: 1/30 Mild GI upset: 4/30	No specific SAEs reported, but 2 patients discontinued	Administration of DMC can inhibit vasopressin secretion following urgery	Postoperative length of stay was not affected by DMC

AE, adverse event; DMC, demeclocycline; GI, gastrointestinal; HN, hyponatraemia; NR, not reported; SAE, serious adverse event; SIADH, symptom of inappropriate antidiuretic hormone secretion.

Table 5 Efficacy and safety results – cohort studies summary

Author, year	Serum sodium (pretreatment)	Serum sodium (post treatment)	Urine sodium (pretreatment)	Urine sodium (post treatment)	AEs (individual)	SAEs (total)	Author conclusion	Comments
De Troyer et al. 1977 (20)	120.4 ± 2.4 mmol/l	135.7 ± 4.2 mmol/l ($p < 0.0005$ vs before)	NR	NR	One patient had a rise in blood urea level Two patients had renal function impairment because of treatment One patient experienced mild nausea	NR	Although DMC moderately impairs renal function, it appears to be the treatment of choice in the chronic form of SIADH	Clinical benefits were reported in five of seven patients
Forrest et al. 1978 (26)	122 mmol/l	139 mmol/l	98 mmol/l	40 mmol/l	NR	NR	DMC is superior to lithium in the treatment of SIADH and may obviate the need for severe water restriction No side effects were observed in this study	Seven patients had carcinoma; one had glioma of the hypothalamus, one had a basal skull fracture and one had SIADH of unknown cause
Goldman and Luchins, 1985 (27)	Mean: 128.1 mmol/l	During treatment, mean: 131.9 mmol/l After treatment, mean: 128.2 mmol/l	NR	NR	NR	NR	DMC reduces the frequency and severity of HN episodes in chronic psychotics	Only five of eight patients met criteria for SIADH
Perks et al. 1979 (22)	118 ± 8 mmol/l	138 ± 7 mmol/l after a mean of 8.6 ± 5.3 days (In six patients who discontinued, serum sodium fell to 125 ± 7 mmol/l)	54 ± 24 mmol/l ($n = 7$)	29 ± 21 mmol/l ($n = 7$)	Eight patients developed azotemia	Two patients discontinued DMC owing to azotemia	The adverse effects of DMC may be more important than previously suggested The 1200 mg dose may be associated with an increased likelihood of impaired renal function	
Brewerton and Jackson, 1994 (28)	Carbamazepine: 130.1 ± 5.9 mmol/l	Carbamazepine plus DMC: 136.7 ± 6.1 mmol/l	NR	NR	NR	NR	DMC appears to have prevented carbamazepine-induced HN in five of six patients	
Trump, 1981 (21)	119 mmol/l	Mean peak serum sodium: 138.8 mmol/l by day 9	92 mmol/l	NR	Azotemia: Serum urea nitrogen > 5 mg/dl: 12	Three patients died within 10 days of	Authors suggest that renal dysfunction associated with DMC	Patients not explicitly diagnosed with SIADH

Table 5 Continued

Author, year	Serum sodium (pretreatment)	Serum sodium (post treatment)	Urine sodium (pretreatment)	Urine sodium (post treatment)	AEs (individual)	SAEs (total)	Author conclusion	Comments
		(peak achieved after 3–28 days)			of 15 patients Serum urea nitrogen > 25 mg/dl: 6 of 15 patients	receiving DMC 1200 mg/day; causes were deemed to be advanced infections or malignancy; all three had marked azotemia	may have contributed to the deaths of three patients Most (five of six) patients with severe azotemia were also receiving other nephrotoxic or antianabolic agents.	

AE, adverse event; CI, confidence interval; CNS, central nervous system; DMC, demeclocycline; GI, gastrointestinal; HN, hyponatraemia; NR, not reported; SAE, serious adverse event; SIADH, symptom of inappropriate antidiuretic hormone secretion

Authors suggested a 1200 mg/day dose may have been too high for the second patient: a 75-year-old woman with decline in general condition and pleural effusion who developed vomiting and diarrhoea on Day 4 of treatment (33).

Overall, most reports suggest that demeclocycline is able to increase serum sodium levels in the majority (60%) of patients with HN secondary to SIADH (12); treatment effectiveness in patients without a specific SIADH diagnosis may be limited (24). The safety profile of demeclocycline appears variable with the potential for complications, such as severe hypernatraemia (39) and renal dysfunction (18). Recent European clinical practice guidelines for diagnosis and treatment of HN recommend against the use of demeclocycline (1). Thus, close monitoring may be warranted in patients receiving demeclocycline for HN secondary to SIADH.

Conclusions

The results from this systematic literature review highlight the paucity of clinical evidence and lack of economic evidence supporting the use of demeclocycline for HN secondary to SIADH. There is a clinical need to treat HN and manage patients with SIADH appropriately (3); in particular, the management of patients with cancer. For example, chemotherapy may need to be delayed until the normalisation of these patients' sodium levels (43), and delays to chemotherapy negatively influence outcomes (44). In addition, some chemotherapy regimens require aggressive hydration strategies (42,45). Furthermore, patients may also require hospital admission for the symptomatic consequences of HN, adding to the burden of their cancer (42,46,47).

Although most reports suggest that demeclocycline can address serum sodium levels in HN (12), efficacy in patients without SIADH may be limited (24). Moreover, with a variable and unreliable time to onset of action, and a safety profile associated with induction of nephrogenic diabetes insipidus, demeclocycline dose adjustments can be complex (12,16). Thus, it may be concluded that patients receiving demeclocycline for HN secondary to SIADH must be closely monitored.

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Table 6 Efficacy and safety results – case reports summary

Author, year	Patient population	Interventions	Outcome	Author conclusion
Antonelli et al. 1993 (29)	A 59-year-old man; slight fever, dyspnoea, weight loss, asthenia and mental slowness	300 mg DMC twice daily for about 3 weeks Water restriction Hypertonic saline iv Corticosteroid treatment for 10 months.	Patient developed phosphate diabetes after 4 days of DMC Progressive amelioration of the symptomatology and resolution of SIADH after DMC discontinuation and the start of corticosteroids	Phosphate diabetes may be related to selective DMC-induced tubulopathy
Curtis et al. 2002 (30)	A 94-year-old man hospitalised following collapse Diagnosis of SIADH	300 mg DMC three times daily plus fluid restriction Nine days after admission, DMC increased to four times daily Metronizadole Benzydamine hydrochloride mouth washes	Fatal acute renal failure	Short-term DMC can effectively control symptomatic HN but caution is required because of its potential nephrotoxicity Authors note a danger of dehydration in patients whose fluid intake has become compromised Authors suggest that had DMC been discontinued once the HN had resolved, the development of acute renal failure would have been avoided
Danovitch et al. 1978 (31)	Two patients: 1. A 51-year-old man with oat-cell carcinoma of the lung. Diagnosis of SIADH 2. A 60-year-old-man with 4-week history of confusion and drowsiness. Diagnosis of SIADH	1. 1200 mg DMC daily plus cyclophosphamide 2. 1200 mg DMC daily	DMC treatment corrected HN and hypo-osmolality but was discontinued in both patients owing to deterioration of renal function	Potentially dangerous side effects exclude routine use of DMC Overall, DMC is effective in the treatment of SIADH, but has a potential to lead to a deterioration of renal function
Decaux et al. 1981 (33)	A 76-year-old man admitted to hospital because of grand mal seizures SIADH diagnosed	A single dose of DMC Water restriction Urea infusion iv Furosemide	Patient had severe gastric intolerance to DMC and the drug was stopped after the first dose	HN was controlled with furosemide after intolerance to DMC
Decaux et al. 1985 (32)	A 62-year-old woman Heavy smoker reporting weakness and memory loss Diagnosis of SIADH Oat-cell carcinoma	300 mg DMC twice daily	DMC corrected HN but led to phosphate diabetes	Phosphate diabetes appeared after therapy with DMC and persisted for 3 months The augmentation in phosphate clearance was unrelated to serum sodium levels Phosphate diabetes was related to selective DMC-induced renal toxicity
Heim et al. 1977 (34)	75-year-old woman, decline in general condition and pleural effusion (Two further cases not receiving DMC are reported)	DMC 1200 mg/day	HN was corrected by fluid restriction; addition of DMC resulted in increased fluid clearance, but the patient developed vomiting and diarrhoea on day 4 and DMC was stopped on day 7	DMC is a relatively non-toxic antibiotic which was shown to be effective; however, treatment was interrupted on day 8 owing to vomiting and diarrhoea The dose of 1200 mg/day may have been too strong for this patient

Table 6 Continued

Author, year	Patient population	Interventions	Outcome	Author conclusion
Padfield et al. 1978 (35)	A 64-year-old man with SIADH following head injury and meningitis	300 mg DMC four times daily followed by 600 mg DMC four times daily Fixed fluid intake	600 mg DMC four times daily rapidly corrected all biochemical features of SIADH Acute renal failure was possibly induced by DMC On discontinuation of DMC normal renal function returned.	DMC corrected the biochemical abnormalities of SIADH Possible evidence of nephrotoxicity
Perks et al. 1976 (36)	A 61-year-old man with memory deficit Inoperable carcinoma diagnosed 7 months after original admission	600 mg DMC daily Fluid restriction	Treatment with DMC led to clinical and biochemical improvement	DMC is a safe and effective treatment that in this case allowed discharge from hospital This regimen may simplify outpatient management of other patients with this syndrome
Shimoda et al. 1986 (published in Japanese) (38)	A 63-year-old woman hospitalised after losing consciousness; prior surgery for ruptured anterior artery Diagnosis of SIADH	900 mg/day DMC 16 mg/day dexamethasone	Patient became comatose and developed quadriplegia after rapid correction of serum sodium levels Patient died of septic shock after 12 months of hospitalisation	Computed tomography scans and brain stem auditory responses were indicative of ODS
Soudan and Qunibi, 2012 (39)	A 78-year-old woman with history of hypothyroidism, vitiligo, rheumatoid arthritis and early Alzheimer's dementia Hospitalised with severe HN diagnosed as secondary to SIADH.	300 mg DMC three times daily. Fluid restriction Normal saline infusion Furosemide Existing medication: Methotrexate Memantine HCL Mirtazapine Sulfamethoxazole and trimethoprim	Patient developed severe HN as a result of rigid fluid restriction and DMC therapy Serum sodium levels stabilised after discontinuation of DMC	DMC should be reserved for patients unable tolerate or unwilling to follow strict fluid restriction

DMC, demeclocycline; HN, hyponatraemia; ODS, osmotic demyelination syndrome; SIADH, syndrome of inappropriate antidiuretic hormone secretion.

Author contributions

All authors co-wrote and critically reviewed each draft of the manuscript. Penny Dhanjal made recommendations on the original draft plan of inclusion of license and onset of action of demeclocycline as well as a critical review of efficacy and safety data to ensure all relevant adverse events were recorded within the manuscript. All authors contributed to and have approved the final manuscript.

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Appendix A

MESH search strings

Embase

#	Searches	Results
#1	exp inappropriate vasopressin secretion/	2829
#2	syndrome of inappropriate antidiuretic.mp.	1001
#3	(inappropriate antidiuretic adj3 syndrome).mp.	1057
#4	syndrome of immoderate antidiuresis.mp.	0
#5	schwartz-bartter syndrome.mp.	754
#6	hyponatraemia.mp. or exp hyponatraemia/	20,570
#7	hyponatraemia.mp.	2274
#8	sodium ion concentration.mp.	261
#9	sodium serum.mp.	165
#10	sodium blood level.mp. or exp sodium blood level/	9734
#11	hypovolemia.mp. or exp hypovolemia/	11,630
#12	hypovolaemia.mp.	1263
#13	serum osmolality.mp. or exp serum osmolality/	2409
#14	urine osmolality.mp. or exp urine osmolality/	4223
#15	(osmolar or osmolarity).mp.	23,152
#16	exp demeclocycline/ or demeclocycline.mp.	2151
#17	declomycin.mp.	98
#18	declostatin.mp. or exp demeclocycline plus nystatin/	0
#19	ledermycin.mp.	159
#20	demeclotetracycline.mp.	4
#21	(Demeclor or Elkamicina or Fidocin or Mexocine or Novotriclina or Perciclina or Rynabron).mp.	17
#22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	66,834
#23	16 or 17 or 18 or 19 or 20 or 21	2168
#24	**#22 and #23**	**517**

Medline & Medline In-Process

#	Searches	Results
#1	exp Inappropriate ADH Syndrome/ or inappropriate vasopressin secretion.mp.	2,275
#2	syndrome of inappropriate antidiuretic.mp.	754
#3	(inappropriate antidiuretic adj3 syndrome).mp.	811
#4	syndrome of immoderate antidiuresis.mp.	0
#5	schwartz-bartter syndrome.mp.	97
#6	hyponatraemia.mp. or exp hyponatraemia/	9,892
#7	hyponatraemia.mp.	1,707
#8	sodium ion concentration.mp.	231
#9	sodium serum.mp.	104
#10	sodium blood level.mp.	2
#11	hypovolemia.mp. or exp Hypovolemia/	3,954
#12	exp Hypovolemia/ or hypovolaemia.mp.	1,926
#13	hypovolaemia.mp.	983
#14	exp Osmolar Concentration/ or serum osmolality.mp.	60,404
#15	exp Osmolar Concentration/ or ((serum or urine) and osmolality).mp.	62,530

Continued

#	Searches	Results
#16	(osmolar or osmolarity).mp.	53,453
#17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	82,327
#18	demeclocycline.mp. or exp Demeclocycline/	894
#19	declomycin.mp.	13
#20	declostatin.mp.	0
#21	ledermycin.mp.	23
#22	demeclotetracycline.mp.	1
#23	Demeclocyclinum.mp.	0
#24	(Demeclor or Elkamicina or Fidocin or Mexocine or Novotriclina or Perciclina or Rynabron).mp.	4
#25	18 or 19 or 20 or 21 or 22 or 23 or 24	915
#26	**#17 and #25**	**156**

Cochrane Library

#	Searches	Results
#1	MeSH descriptor: [Inappropriate ADH Syndrome] explode all trees	9
#2	inappropriate vasopressin secretion	25
#3	syndrome of inappropriate antidiuretic	19
#4	(inappropriate antidiuretic near/3 syndrome)	16
#5	syndrome of immoderate antidiuresis	0
#6	schwartz-bartter syndrome	0
#7	MeSH descriptor: [Hyponatraemia] explode all trees	107
#8	hyponatraemia or hyponatraemia	526
#9	sodium ion concentration	634
#10	sodium serum	2935
#11	sodium blood level	3870
#12	MeSH descriptor: [Hypovolemia] explode all trees	71
#13	hypovolemia or hypovolaemia	349
#14	MeSH descriptor: [Osmolar Concentration] explode all trees	1233
#15	serum osmolality	298
#16	((serum or urine) and osmolality)	503
#17	osmolar or osmolarity	1638
#18	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17	8019
#19	MeSH descriptor: [Demeclocycline] explode all trees	45
#20	demeclocycline	68
#21	declomycin or declostatin	0
#22	ledermycin or demeclotetracycline or Demeclocyclinum	12
#23	Demeclor or Elkamicina or Fidocin or Mexocine or Novotriclina or Perciclina or Rynabron	0
#24	#19 or #20 or #21 or #22 or #23	78
#25	**#18 and #24**	**6**

Appendix B

Summaries of excluded full-length papers

Reference	Exclusion reason
Boissonnas A, Casassus P, Caquet R, Laroche C. Hyponatraemia in a cirrhotic suffering from late cutaneous porphyria: A drug to avoid, demeclocycline. [French]. Nouvelle Presse Medicale 1979; 8(3): 210.	Not SIADH
Burst V, Verbalis J, Greenberg A et al. Hyponatraemia in the hospital setting: Interim results from a prospective, observational, multi-center, global registry. Pneumologie Conference 2013; 54.	Conference abstract – no full text available
Cawley MJ. Hyponatraemia: Current treatment strategies and the role of vasopressin antagonists. Annals of Pharmacotherapy 2007; 41(5): 840–50.	Review with no relevant data
Jellett L, O'Hare J, McAleese J. Syndrome of inappropriate antidiuretic hormone (SIADH) in patients with small cell lung cancer & incidence and response to treatment. Lung Cancer 2011;Conference: 9th Annual BTOG Conference 2011 Dublin Ireland. Conference Publication: 71: S41.	Conference abstract – no full text available
Kamoi K, Ebe T, Kobayashi O et al. Atrial natriuretic peptide in patients with the syndrome of inappropriate antidiuretic hormone secretion and with diabetes insipidus. Journal of Clinical Endocrinology and Metabolism 1990; 70(5):1385–90.	Small case study – three patients treated and no safety issues reported
Kamoi K, Toyama M, Takagi M et al. Osmoregulation of vasopressin secretion in patients with the syndrome of inappropriate antidiuresis associated with central nervous system disorders. Endocrine Journal 1999; 46(2): 269–77.	No specific demeclocycline results
Laszlo FA, Varga C, Doczi T. Cerebral oedema after subarachnoid haemorrhage. Pathogenetic significance of vasopressin. Acta Neurochirurgica 1995; 133 (3–4): 122–33.	No treatment data
Miller PD, Linas SL, Schrier RW. Plasma demeclocycline levels and nephrotoxicity. Correlation in hyponatremic cirrhotic patients. JAMA 1980; 243(24): 2513–5.	Not SIADH
Nagler EV, Haller MC, Van Biesen W et al. Treatments for chronic hyponatraemia: A systematic review of randomised controlled trials. Nephrology Dialysis Transplantation 2013;Conference: 50th ERA-EDTA Congress Istanbul Turkey. Conference Publication: 28: i387.	Conference abstract – no full text available
Philip T, Souillet G, Gharib C et al. Inappropriate secretion of antiduiuretic hormone during acute leukaemia treated with vincristine. Two cases (author's transl). [French]. La Nouvelle presse medicale 1979; 8(26): 2181–5.	Small case study – one patients treated and no safety issues reported
Shakher J, Thompson J. Tolvaptan cost effective treatment of SIADH in malignancies. Lung Cancer 2013;Conference: 11th Annual British Thoracic Oncology Group Conference, BTOG 2013 Dublin Ireland. Conference Publication: 79: S66.	Conference abstract – no full text available
Walter HS, Ahmed SI. The incidence of hyponatraemia in small cell lung cancer: Prognostic and predictive potential in a retrospective single centre analysis. Lung Cancer 2013;Conference: 11th Annual British Thoracic Oncology Group Conference, BTOG 2013 Dublin Ireland. Conference Publication: 79: S65–S6.	Conference abstract – no full text available

Appendix C

Quality assessments

Quality assessment of included randomised controlled trials

Quality assessment question	Yes/No/ Unclear/NA	Notes
Alexander RC et al. 1991 (24)		
Internal validity		
Does the study address an appropriate and clearly focused question?	Yes	Quote: 'we undertook a double-blind, placebo-controlled study of demeclocycline in psychiatric patients with polydipsia-hyponatraemia'
Is the assignment of subjects to treatment groups randomised?	Yes	Order of treatment was randomly assigned; study used a cross-over method
Is an adequate concealment method used?	Unclear	Study was double-blind and placebo-controlled, but details on method of concealment were unclear
Are subjects and investigators kept 'blind' about treatment allocation?	Unclear	Study was double-blind and placebo-controlled, but details on method of blinding were unclear

Continued

Quality assessment question	Yes/No/ Unclear/NA	Notes
Are the treatment and control groups similar at the start of the trial?	NA	Crossover design, not applicable
Is the only difference between groups the treatment under investigation?	Yes	Crossover design; groups are identical aside from order of treatment
Are all relevant outcomes measured in a standard, valid and reliable way?	Yes	Quote: 'serum sodium levels were obtained in the morning twice a week (routine sodium levels) and also following episodes of acute weight gain (sporadic sodium levels)'Further details on serum sampling and sodium measurement not provided
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		No patients dropped out
Are all the subjects analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis)?	NA	Crossover design, not applicable
Where the study is carried out at more than one site, are results comparable for all sites?	NA	Single site study
Overall assessment		
How well was the study done to minimise bias? (high quality/acceptable/reject)		
Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?		
Are the results of this study directly applicable to the patient group targeted by this guideline?		
Horratas MC et al. 1998 (25)		
Internal validity		
Does the study address an appropriate and clearly focused question?		
Is the assignment of subjects to treatment groups randomised?	Yes	Patients were randomly assigned to treatment or placebo; details of exact method used to randomise not reported
Is an adequate concealment method used?	Unclear	Study was double-blind and placebo-controlled, but details on method of concealment were unclear
Are subjects and investigators kept 'blind' about treatment allocation?	Yes	Quote: 'Neither the patients, caregivers, nor the investigators were aware of the assigned patient group. The study was blinded until its completion.'
Are the treatment and control groups similar at the start of the trial?	Unclear	No summary of baseline characteristics providedQuote: 'the two groups remained matched for age, sex, and weight'
Is the only difference between groups the treatment under investigation?	Unclear	Exclusion criteria were defined and many patients not included if they had certain comorbidities, but insufficient information provided on baseline characteristics of included patients
Are all relevant outcomes measured in a standard, valid and reliable way?	Unclear	Limited information on outcome collection; authors state there is no commercial assay for demeclocycline
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		Two patients in the demeclocycline group discontinued (2/15; 13.3%); no patients in the placebo group discontinued
Are all the subjects analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis)?	No	No mention of intention-to-treat analysis analysis; it appears the two patients who dropped out were not included in the analysis
Where the study is carried out at more than one site, are results comparable for all sites?	NA	Single site study
Overall assessment		
How well was the study done to minimise bias? (high quality/acceptable/reject)		
Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?		
Are the results of this study directly applicable to the patient group targeted by this guideline?		

Quality assessment of included cohort studies

Quality assessment question	Yes/No/ Unclear	Notes
Brewerton T et al. 1994 (28)		
Internal validity		
Does the study address an appropriate and clearly focused question?	Yes	Quote: 'We would like to extend these observations of demeclocycline's reversal of carbamazepine-induced hyponatraemia in a group of six psychiatric inpatients'
Are the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	NA	Single cohort/case series; no controls
Does the study indicate how many of the people asked to take part did so, in each of the groups being studied?	NA	Retrospective analysis of single cohort/case series; no controls
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	NA	All patients had a diagnosis of hyponatraemia (< 135 mmol/l) while taking carbamazepine and were subsequently treated with demeclocycline
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		Retrospective analysis; all patients completed
Is the comparison made between full participants and those lost to follow up, by exposure status?	NA	No patients lost to follow-up
Are the outcomes clearly defined?	Yes	
Is the assessment of outcome made blind to exposure status? (if the study is retrospective this may not be applicable)	NA	Retrospective analysis
Where blinding was not possible, is there some recognition that knowledge of exposure status could have influenced the assessment of outcome?	No	
Is the method of assessment of exposure is reliable?	Yes	Chart review
Is evidence from other sources used to demonstrate that the method of outcome assessment is valid and reliable?	No	
Is the exposure level or prognostic factor assessed more than once?	No	
Are the main potential confounders identified and taken into account in the design and analysis?	No	
Have confidence intervals been provided?	No	Confidence intervals not provided but standard deviations reported
De Troyer A, 1977 (20)		
Internal validity		
Does the study address an appropriate and clearly focused question?	Yes	Aim of study was to test 'the efficacy of demeclocycline hydrochloride in suppressing the tubular action of tumoral antidiuretic products'
Are the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	NA	Single cohort/case series; no controls
Does the study indicate how many of the people asked to take part did so, in each of the groups being studied?	No	Patients were consecutive, but unclear if any patients were asked to take part and did not provide consent
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	NA	All patients had SIADH at the start of the trial; no separate control group
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		No patients lost to follow-up
Is the comparison made between full participants and those lost to follow up, by exposure status?	NA	No patients lost to follow-up
Are the outcomes clearly defined?	Yes	
Is the assessment of outcome made blind to exposure status? (if the study is retrospective this may not be applicable)	No	
Where blinding was not possible, is there some recognition that knowledge of exposure status could have influenced the assessment of outcome?	No	
Is the method of assessment of exposure is reliable?	Yes	No other therapy given throughout the study; fluid and sodium intake *ad libitum*

Continued

Quality assessment question	Yes/No/ Unclear	Notes
Is evidence from other sources used to demonstrate that the method of outcome assessment is valid and reliable?	No	
Is the exposure level or prognostic factor assessed more than once?	No	
Are the main potential confounders identified and taken into account in the design and analysis?	No	
Have confidence intervals been provided?	No	Confidence intervals not provided but standard deviations reported
Forrest JN et al. 1978 (26)		
Internal validity		
Does the study address an appropriate and clearly focused question?	Yes	Quote: 'We compared the responses to demeclocycline and lithium in a series of 10 patients with [SIADH]'
Are the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	NA	Single cohort/case series; no controls
Does the study indicate how many of the people asked to take part did so, in each of the groups being studied?	NA	Retrospective analysis of single cohort/case series; no controls
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	NA	All patients had chronic SIADH as identified by medical records
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		Retrospective analysis; all patients completed
Is the comparison made between full participants and those lost to follow up, by exposure status?	NA	No patients lost to follow-up
Are the outcomes clearly defined?	Yes	
Is the assessment of outcome made blind to exposure status? (if the study is retrospective this may not be applicable)	No	Retrospective analysis
Where blinding was not possible, is there some recognition that knowledge of exposure status could have influenced the assessment of outcome?	No	
Is the method of assessment of exposure is reliable?	Yes	Chart review
Is evidence from other sources used to demonstrate that the method of outcome assessment is valid and reliable?	No	
Is the exposure level or prognostic factor assessed more than once?	No	
Are the main potential confounders identified and taken into account in the design and analysis?	No	Some patients received lithium prior to demeclocycline and others did not; unclear if proper washout period undertaken
Have confidence intervals been provided?	No	Confidence intervals not provided but standard errors of the mean reported (graph only)
Goldman MB et al. 1985 (27)		
Internal validity		
Does the study address an appropriate and clearly focused question?	Yes	The study attempts to replicate previous findings from a case report using a larger sample size
Are the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	NA	Single cohort/case series; no controls
Does the study indicate how many of the people asked to take part did so, in each of the groups being studied?	Unclear	Unclear if any patients refused to participate
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	Unclear	All patients had hyponatraemia at time of enrolment but only 5/8 met criteria for SIADH
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		No patients lost to follow-up
Is the comparison made between full participants and those lost to follow up, by exposure status?	NA	No patients lost to follow-up
Are the outcomes clearly defined?	Yes	
Is the assessment of outcome made blind to exposure status? (if the study is retrospective this may not be applicable)	No	
Where blinding was not possible, is there some recognition that knowledge of exposure status could have influenced the assessment of outcome?	No	

Continued

Quality assessment question	Yes/No/ Unclear	Notes
Is the method of assessment of exposure is reliable?	Yes	
Is evidence from other sources used to demonstrate that the method of outcome assessment is valid and reliable?	No	
Is the exposure level or prognostic factor assessed more than once?	No	
Are the main potential confounders identified and taken into account in the design and analysis?	No	
Have confidence intervals been provided?	No	Confidence intervals not provided but standard deviations reported
Perks WH et al. 1979 (22)		
Internal validity		
Does the study address an appropriate and clearly focused question?	Yes	The authors determined the effect of demeclocycline on patients with SIADH, especially renal function
Are the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	NA	Single cohort/case series; no controls
Does the study indicate how many of the people asked to take part did so, in each of the groups being studied?	Unclear	Unclear if any patients refused to participate
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	NA	All patients had SIADH based on specific criteria
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		7/14 patients (50%) discontinued, including one death, however it appears that all patients were taking demeclocycline at the analysis timepoint of 10 days
Is the comparison made between full participants and those lost to follow up, by exposure status?	Unclear	Only comparison between serum sodium levels in all patients (pre-discontinuation) are compared with levels in patients who discontinued
Are the outcomes clearly defined?	Yes	
Is the assessment of outcome made blind to exposure status? (if the study is retrospective this may not be applicable)	No	
Where blinding was not possible, is there some recognition that knowledge of exposure status could have influenced the assessment of outcome?	No	
Is the method of assessment of exposure is reliable?	Yes	
Is evidence from other sources used to demonstrate that the method of outcome assessment is valid and reliable?	No	
Is the exposure level or prognostic factor assessed more than once?	No	
Are the main potential confounders identified and taken into account in the design and analysis?	Unclear	Discontinuation is taken into account during analysis; no indication of other confounding factors accounted for
Have confidence intervals been provided?	No	Confidence intervals not provided but standard deviations reported
Trump DL et al. 1981 (21)		
Internal validity		
Does the study address an appropriate and clearly focused question?	Yes	To assess the efficacy of demeclocycline in the treatment of patients with water intoxication and cancer
Are the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	NA	Single cohort/case series; no controls
Does the study indicate how many of the people who asked to take part did so, in each of the groups being studied?	NA	Retrospective analysis of single cohort/case series; no controls
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis?	NA	All patients had cancer and hyponatraemia as identified by medical records
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?		Retrospective analysis; all patients completed
Is the comparison made between full participants and those lost to follow up, by exposure status?	NA	No patients lost to follow up
Are the outcomes clearly defined?	Yes	
Is the assessment of outcome made blind to exposure status? (if the study is retrospective this may not be applicable)	No	Retrospective analysis
	No	

Continued

Quality assessment question	Yes/No/ Unclear	Notes
Where blinding was not possible, is there some recognition that knowledge of exposure status could have influenced the assessment of outcome?		
Is the method of assessment of exposure is reliable?	Yes	Chart review
Is evidence from other sources used to demonstrate that the method of outcome assessment is valid and reliable?	No	
Is the exposure level or prognostic factor assessed more than once?	No	
Are the main potential confounders identified and taken into account in the design and analysis?	No	All patients had different total doses of demeclocycline and different treatment periods; these are listed but not accounted for in the analysis
Have confidence intervals been provided?	No	Confidence intervals not provided but ranges reported