

Review article

“Efficacy of Combination drug therapy of Oxybutynin and Desmopressin in enuresis in children in comparison to one drug therapy or any other combination drug therapy : A Systematic review and Meta-analysis”

Rita Hajela¹, Rajeev Vinayak², Hemant Gupta³

Abstract:

Background: This Systematic review was undertaken to bring forward some solution to the old stubborn neglected problem of enuresis in children which appears to be left out in the race of scientific advancements. The pathogenesis of disease so far understood is supposed to be the result of three factors of Polyuria, Overactive bladder and difficulties in arousal from sleep. However pinpointing the extent and role of each one in an individual case is a difficult time and resource consuming job. The aim of study is to help front line clinicians in decision making in poor resource limited developing countries, so that children and families are not abandoned to suffer on their own without any hope for a speedy solution, when they come forward asking for help. **Methods:** We hypothesized that combination therapy of Desmopressin and oxybutynin in usual therapeutic doses at outset, might be a solution. To accumulate evidence an extensive search was done as per PRISMA 2020 guideline for properly designed double blind Randomized clinical trials to back up any such decision. Databases searched were PubMed, Embase, Google Scholar, Scopus and web of science. Clinical trial registry platforms, open access grey areas and cross references were also searched. Data obtained was analyzed by random effect model , at 95% confidence interval with Mantel Haenszel test for risk ratio. Protocol was registered at PROSPERO **Results:** There was lack of robust randomized data for any nodal network meta-analysis. Nine studies were included for analysis having experimental or Intervention arm as combination therapy versus Desmopressin mono drug therapy as comparator. Synthesis of data and meta-analysis was done using Cochrane Revman version 5.4 There was lack of studies for comparison to Oxybutynin and Imipramine mono drug therapy, hence they are discussed in tabular form only There is some hope in other combinations also in new entrants in the armamentarium against enuresis in children like Tolterodine, Solifenacin, Propiverine. A favorable outcome was observed for this combination therapy at outset in whatever studies we found, but risk of bias is there and superiority can be said as only marginal. More robust evidence is needed from scientific researchers for different pharmacological combination therapies at outset to decrease the gap from the point of seeking help to control of enuresis. **Conclusion:** We recommend trial of Desmopressin Oxybutynin combination therapy at the time of seeking help in resource poor developing countries to tackle this stigmatized socially unacceptable problem of children at present. This will also help in generating more robust data in favor or against any such decision for future reference and analysis. But we can say that the scientific fraternity is still far behind in properly designed randomized and blinded trials for any clear and evidence based medicine for this entity.

Keywords : Enuresis , Desmopressin, Oxybutynin, Combination therapy, Children

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Introduction

Enuresis is the term used for bed wetting or intermittent urinary incontinence or involuntary passage of urine in a child more than 5 years of age

while asleep, irrespective of its limitation to night time or concomitance with day time, irrespective of underlying pathology or cytometric evaluation results¹, further subdivided into monosymptomatic

1. Dr. Rita Hajela, MD Pediatrics, Professor, Department of Pediatrics, Maharishi Markandeshwar Medical college and Hospital, Kumahatti, Solan, 173229, Himachal Pradesh, India, E mail hajelarita@gmail.com
2. Dr. Rajeev Vinayak, MD Pediatrics, Professor, Department of Pediatrics, Maharishi Markandeshwar Medical college and Hospital, Kumahatti, Solan, 173229, Himachal Pradesh, India. E mail 000rjv@gmail.com Mobile +91 9805158754
3. Dr. Hemant Gupta, MD Pediatrics , Associate Professor, Department of Pediatrics, Maharishi Markandeshwar Medical college and Hospital, Kumahatti, Solan, 173229, Himachal Pradesh, India, E mail hemant.solan@gmail.com Mobile +919418469707

Correspondence: Dr. Rita Hajela, Professor, Department of Pediatrics, Maharishi Markandeshwar Medical college and Hospital, Kumahatti, Solan, 173229, Himachal Pradesh, India, E mail hajelarita@gmail.com , Mobile +91 9518848820

(MNE) and non monosymptomatic (NMNE) variety. NMNE children additionally have other lower urinary tract symptoms (LUTS) like daytime incontinence, urgency, voiding difficulties or abnormally low or high urinary frequency. It is a common problem in children and adolescents but is under reported. An increase in incidence of enuresis has been noted in various parts of world during current pandemic. Yale New Haven Children's Hospital has reported a spike in day and nighttime wetting since the start of the COVID-19 outbreak. It may be due to an increase in anxiety and depression among children, one of the unintended consequences of mental health issues arising out of pandemic management strategies or it could be a presentation of Covid-19 related neuropathy. We may understand it better as our understanding of Covid -19 pandemic improves.²

Child is developmentally ready for toilet training between 2-4 years of age. By 5 years of age 90-95% children are continent during day and 80-85% by night, remaining 15-20% do suffer from bed wetting and its consequences. In spite of this being an alarming percentage, Enuresis remains a neglected clinical condition both by family and by clinicians. It is considered a harmless entity although it has large psychological and social implications. Impact on emotional state of child is immense, confidence and self esteem is affected greatly, feeling of failure, rejection from peers, bullying result into a state of chronic stress. Emotional trauma, inability to participate in social events, school outings may hamper child's development. Such children are also likely to become victim of corporal punishment, child abuse and rejection from family members and relatives.³ Treatment is usually sought very late and only in desperate frustrating situations. A social stigma and taboo is associated with it, matter is not discussed openly. Problem is either left to heal with time or local herbal treatments are tried at home like kratom. Kratom is a herbal opioid and mood elevator and is used in many parts of world to treat sleep disorders. In higher doses it may itself cause bed wetting, here methadone may be of help.⁴

When left to time for achieving normalcy, children usually take years to become continent, while precious developmental years of life get affected and psychological damage done. Moreover chance of becoming dry without treatment is very low if frequency of bed wetting is high. Scientific evidence supports that children who become completely dry have higher self esteem than those with persistent

enuresis.⁵ Therefore there is a need to encourage both parents as well as primary care doctors to seek and start effective treatment early in the course of disease for the welfare of children as well as society.

Pathophysiology of enuresis is still not clearly understood, several factors are considered contributory. Nocturnal polyuria, a result of ADH deficiency, circadian rhythm failure, reduced nocturnal functional bladder capacity or overactive bladder and impaired arousal from sleep in response to full bladder are attributed.^{6,7} Any factor may be a major contributor in an individual, however finding that factor is a tedious job although it decides success of a treatment. Currently treatment revolves around nonpharmacological and pharmacological approaches, but success is limited whatever approach is used. Lack of short term effective pharmacotherapy, cumbersome rituals in behavior and alarm therapy, dry bed training, star charts, sequential treatment approach of long duration are contributing to persistence of this problem as an ongoing challenge.⁸ Treatment itself is not simple, a tiring long journey of instructions to follow, rituals to be done, diaries to maintain with no immediate relief in sight are in store. So far alarm therapy is considered the best with a success of 66-77 percent.⁹ This is also not easily available in developing countries and may not be affordable by many belonging to poor socioeconomic status.

Amongst the pharmacological interventions Desmopressin, anticholinergics and antimuscurinics or their various combinations are in use. The path is slow, sequential and frustrating, with addition of one thing at a time, waiting for that therapy to fail and then another to be tried. Desmopressin, Oxybutynin (Anticholinergic) and Imipramine (tricyclic antidepressant), all three having different modes of action are most commonly used but without any one being clearly better than other. Therefore chances of success with a combination therapy appears theoretically possible. Desmopressin is recommended as first line, addition of second drug is recommended once desmopressin fails. Anticholinergics are further classified according to the receptor they act upon, called as Antimuscarinic and Antinicotinic, operating upon muscarinic acetylcholine receptors and nicotinic acetylcholine receptors respectively. Antimuscurinics approved for treatment of Overactive bladder (OAB) are Oxybutynin, Tolterodine, Propiverine, Solifenacin etc. Oxybutynin was the first antimuscarinic used in

enuresis and is still the most popular drug.

For individualization of treatment vasopressin level estimations, urodynamic studies, uroflowmetry, post voidal residual volume measurement of urine are needed. A lot of time, money and resources are involved, along with a lengthy pretreatment phase. Parents usually do not have such patience and compliance for a non life threatening illness. Giving up to situation and abandonment of treatment is the usual outcome.

Results of a single drug therapy are far from satisfactory. Desmopressin is in use for about last 50 years with static results and relapse. Evidence has been found in many studies that addition of a second drug improves success rate, bringing complete cure in larger proportion. Improvement occurs earlier, therefore speed of control is also faster. The same happens to proportion of cases showing partial improvement as compared to failure. As of today pharmacotherapy is a sequential process. Quick response is a desirable goal to minimize psychological damage and rebuilding of self-esteem of child. Therefore interest has recently arisen for use of combination pharmacotherapy early in the course of this multimodal entity.¹⁰

Clinical decision in an individual case depends on many factors especially the AFASS criteria of being Acceptable, Feasible, Affordable, Sustainable and Safe. AFASS criteria may not be totally scientific but is the practical answer especially in developing and poor countries. The present systematic review and meta-analysis is undertaken to gather evidence regarding use of combination therapy of Desmopressin and Oxybutynin especially if establishing the predominant factor in a given child is difficult. Combination of Desmopressin and oxybutynin was chosen as success of both have been established to some extent separately. In this review we set out to answer our research question, "Is Oxybutynin desmopressin combination therapy better than Oxybutynin or desmopressin or imipramine or any other drug alone or any combination of other drugs in treatment of enuresis/nocturnal enuresis in children."

Material and methods

The systematic review was done in line with PRISMA 2020 statement, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.¹¹ The protocol was prepared after thoroughly studying the methods of systematic review and meta-analysis, further strengthened by Cochrane handbook

and taking guidance from library internet sites in preparing search strategies. The protocol was registered at PROSPERO international registry vide no CRD42021238844

Search strategy

A systematic search using PICO model (Population, Intervention, Comparator, Outcome) was performed to identify potential published studies on human subjects for inclusion in the systematic review. Keywords, controlled vocabulary, subject terms, entry terms, text words, MeSH terms and Emtree terms considering major headings, subheadings, supplementary concept and explode feature were used. Both simple and complex searches were done with advanced search builders. The search was limited to English language. No date filter was applied, wherever necessary, search was limited from 1989 till date. Search was performed in month of March and April 2021 and rerun in first few days of May 2021. Two authors performed search independently and matched their results later. Reproducibility of results was checked during search rerun.

PICO model was prepared for PubMed search, Outcome was not used in performing search. The focus area was Title Abstract and keywords. When there were zero or limited results, all fields were considered. Our Inclusion criteria for population was children more than 5 years of age or adolescents up to 18 years of age suffering from Enuresis/nocturnal enuresis. For ease of search and applicability in different databases studies were included from 0-18 years, to be excluded later on if it did not meet our inclusion criteria, so that any borderline study with age variation is not missed. Intervention was defined as combination of Desmopressin and Oxybutynin treatment used at any stage of disease. Drugs used in Comparator arm were Desmopressin, Oxybutynin, Imipramine, Tolterodine, Solifenacin, Propiverine, Reboxetine, Atomoxetine and Mirabegron. Search was repeated with different comparators in one arm. The keywords used for population were Enuresis OR Nocturnal enuresis OR Diurnal enuresis OR urinary incontinence OR Bed wetting OR day time urinary incontinence OR nighttime urinary incontinence OR Nocturia OR Nocturnal polyuria OR enuresis nocturnal OR enuresis diurnal. For Intervention Key terms used were Desmopressin OR Deamino Arginine Vasopressin, OR 1-Deamino-8-D-arginine Vasopressin OR 1-Desamino-8-arginine Vasopressin OR Adiuretin OR Adiuretin SD OR Apo-Desmopressin OR DDAVP OR Desmogalen

OR Desmopressin Acetate OR Desmopressin Monoacetate OR Desmopressin Monoacetate, Trihydrate OR Desmopressine Ferring OR Desmospray OR Desmotabs OR Minirin OR Minurin OR Nocutil OR Octim OR Octostim OR Vasopressin OR Deamino Arginine . Similar strategy was used for, Oxybutynin, Imipramine, Tolterodine, Solifenacin, Propiverine, Reboxetine, Atomoxetine and Mirabegron, considering all available entry terms and synonyms. Strategy was later adapted and modified for each database. Automatic Filters of Clinical trial, Randomized controlled trial RCT and Child up to 18 years were used to identify potential studies quickly , although data was collected without filters and manually hand searched through abstract reading for any missing study. Alerts for new information were also created wherever available.

Databases searched

Search was performed on multiple databases for comprehensiveness. PubMed/ Medline, Embase, Google scholar, Scopus and Web of science. Cochrane database was included for Systematic reviews for hand searching their bibliography. Clinical trial registry platforms were searched at www.clinicaltrials.gov and at Cochrane central registry of controlled trials (CENTRAL). World health organization clinical trial registry platform at WHO portal www.who.int/ictrp/en., ongoing trials were searched at, www.centerwatch.com, www.controlled-trials.com , Drugs & FDA sites www.fda.gov/scripts/cder. We also searched Indian sites for drug trial registry CTRI at <http://ctri.nic.in/Clinicaltrials>. Indian thesis site shodhganga and Shodhgangotri were also searched. Hand searching was performed in Nephrology, Urology and Pediatric journal indexes. Conference proceedings were searched at crossref. Bibliographies of relevant studies were also hand searched. Open access platforms for grey literature were searched at Proquest and OpenGrey. Number of Search results were documented and tabulated in a word file. Zotero software was used for collection of search results. End note software was also used.

Identification of Included studies

The major criteria for considering any study for further analysis was Combination drug therapy in intervention arm at any stage of treatment of enuresis in children. Initially only RCT were sought but due to paucity of data both in number of studies and number of participants in each study, lack of description of randomization process in most studies, claimed

to be RCT, we decided to broaden our review to include prospective clinical trials also with risk for randomization being part of risk of bias assessment, so that our readers can infer results accordingly. PRISMA flow diagram appended below describes the process. AND Boolean operator was used between Desmopressin, oxybutynin but when results were zero OR Boolean operator was also used for comprehensiveness. To ensure that we did not miss any studies only population (Enuresis) search was also made at clinical trial registry platforms. PICO search was performed at all sites but only few results were obtained. When only population (Enuresis) was searched, many results were found, but they all proved to be irrelevant for inclusion leading to exclusion of many comparator arms.

Exclusion criteria

Reason 1: Intervention arm did not use combination of Desmopressin and Oxybutynin together

Reason 2 : Study design was neither a prospective clinical trial nor a randomized controlled trial.

Reason 3 : Study was conducted on Adults or geriatric patients

Reason 4 : Other combination therapies but they did not compare to drug combination under review

Reason 5 : Outcome measured is different

Identification of studies

Databases PubMed n=65, Embase n= 69 ,Google scholar n = 13, Scopus n = 63, web of science n = 19 (limited to last 5 years)

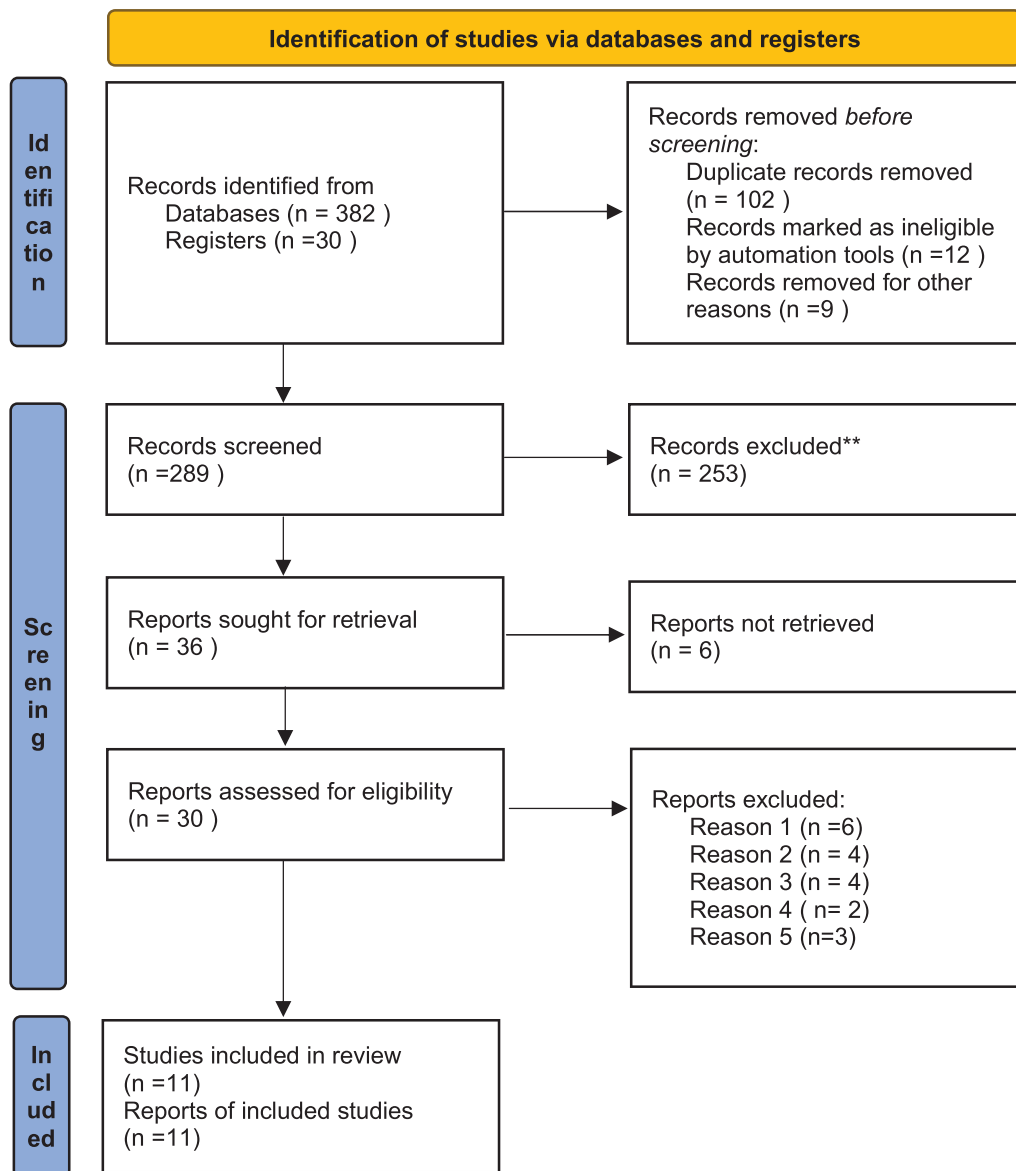
ProQuest n=152, Total = 382, Clinical trials ,Cochrane CENTRAL trial database n=19, clinicaltrials.gov n=2 ,WHO (ICTRP) n= 0, fda n= 7, ISRCTN (British) n=0, Indian sites n=0, journal search and hand searching and alerts =2, Total = 30 , cross references search at crossref n= 6320 (for hand searching)

Studies included are shortened here as Intervention /Experiment arm A = Combination therapy of Desmopressin and Oxybutynin , B = Desmopressin monotherapy C= Oxybutynin monotherapy, D = Imipramine monotherapy, E = Tolterodine, F= Propiverine ,G= Solifenacin ,H= Atomoxetine , I= Reboxetine, J = Mirabegron

Primary Outcomes to be measured as per study protocol were

1. Success or failure as dichotomous variables

PRISMA flow diagram 2020 for systematic reviews



2. Complete response or partial response
3. Percentage decrease in frequency of Bed wetting after initiation therapy in next three months or as given in study

Additional outcomes

1. Frequency of Bed wetting after initiation of therapy in next three months or as given in study
2. Frequency of bed wetting after cessation of interventional therapy
3. Permanence of effect as measured six months after cessation of interventional therapy if available
4. Adverse effect of interventional therapy

Complete response was taken as complete cessation or more than 90% reduction from baseline frequency of wet nights. Partial response as more than 50% reduction (50-90%) from baseline frequency. Failure as less than 50% reduction in wet episodes from baseline.

Data analysis and Synthesis of data

9 studies were included for analysis of outcomes in combination therapy as Intervention and Desmopressin as comparator We found that there were two type of studies one which used combination therapy at the outset, others which introduced combination therapy once desmopressin alone

failed. There was paucity of data in groups where this combination therapy was compared to other single drug therapies or combination drug therapies as planned (C, D, E,)therefore we will discuss them one by one in tabular form, but no synthesis of data or network meta-analysis was possible for them. No study was found which compared (F,G,H,I) with our combination therapy. Therefore synthesis of data has been done for comparator as Desmopressin monotherapy only . Results were collected from studies as basic numbers for homogenization of data. Where data was given as percentage, it was converted back to basic number for comparability with other studies. Response parameters were included on four aspects for speed, measured as complete response at 1 month , permanence as complete response at 3 months, efficacy as total response at 3 months and tolerability as adverse effects leading to cessation of therapy. Other outcomes as planned in protocol could not be measured as most of studies did not mention them clearly although some described them. Frequency of bed wetting after cessation of interventional therapy, which is an important outcome was also not available in most of studies and therefore omitted from synthesis. However

it was clear from various studies, that problem of enuresis needs long term treatment and therapy has to be continued for about 6 months or more and gradual withdrawal is recommended, early cessation of therapy or abrupt withdrawal is marked with relapse

If responses were not measured at 1 month and 3 month of therapy in the study and response was measured in weeks, 4 weeks was considered as 1 month and more than 4 weeks was considered as response at 3 months for data synthesis. If published data has been so modified so, it is mentioned by an asterisk sign before study for readers knowledge. We had to adopt this path because of paucity of data on the subject and to initiate well designed multiple trials globally to collect more robust evidence. If the pure raw data is still ambiguous and not acceptable the study has been excluded from the systematic review at the stage of data synthesis also. Data was extracted from individual studies into Microsoft excel sheet. Risk of Bias assessment was done as per Cochrane Risk of bias tool. Data was synthesized in Cochrane review manager tool RevMan 5.4. Study characteristics are mentioned in **Table 1 and 2**

Table 1 : Study characteristics of included studies in Combination versus Desmopressin monotherapy

S.no.	Author, Year, location, Reference	Type of patient	Study Type	Age group	Efficacy, duration (months)	Entry time	Combination of drug, dose	Number Intervention /Control
1	Kazi A, 2020, Pakistan, (12)	MNE	RCT,	7-13	1,2,3	Begin	(A)0.2mg desmopressin tab +5 mg Oxybutynin (B) 0.2mg desmopressin	n=84, 42/42
2	Ravanshad Y 2017, Iran (13)	MNE	RCT,	5-15	1,2,3	Begin	(A)20 µm I/N desmopressin +5mg Oxybutynin (B) 20 µm I/N desmopressin	n=59 30/29
3	Almsafer MM 2017, Iraq (14)	MNE	RCT	6-14	1,3	Begin	(A)20 µm I/N desmopressin + 5 mg Oxybutynin (B) 20 µm I/N desmopressin	n=41 20/21
4	Azhir A, 2008, Iran(15)	MNE	CT	6-12	1,3	Begin	(A) 0.1mg desmopressin tab + 5 mg oxybutynin (B) 0.1mg desmopressin tab	n=31 10/16
5	Lee T, 2005, Korea, (16)	MNE/ Poly both	RCT	6-15	1,3,6	Begin	(A) 0.1-0.2 mg Desmopressin + 5mg Oxybutynin (B) 0.2-0.4mg Desmopressin	n=97 48/49

S.no.	Author, Year, location, Reference	Type of patient	Study Type	Age group	Efficacy, duration (months)	Entry time	Combination of drug, dose	Number Intervention /Control
6	Caione P, 1997, Italy (17)	MNE/poly	CT	6-24	1,2,5	Begin	(A)30 µm I/N DDAVP spray , 0.2 mg/kg oxybutynin, (B) 30 µm I/N DDAVP	n=114 24/66
7	Montaldo P 2011,Italy (18)	MNE	RCT, Stratified Double blinding	6-13	1	failed	(A)240 µg, desmopressin + 5mg Oxybutynin (B) 240 µg, desmopressin + Placebo	n=120 61/59
8	T Neveus et.al. 1999, Sweden(19)	MNE	3 period cross over CT	6-16	2 weeks	failed	(A) 0.4 mg Desmopressin+ 5mg oxybutynin, (B) 0.8mg desmopressin	n=33 24/9
9	E Radvanksha 2006, Denmark (20)	MNE	CT (sequential)	6-15	2 week, 2 week	failed	(A) 20 µg Desmopressin + 5 mg Oxybutynin (B) 20 µg Desmopressin	n=60 19/60

Table 2: Summary data of included studies for Combination versus Desmopressin monotherapy

S.no.	Author,Year, location, Reference	Number Intervention /Control	Outcome 1 (Speed) complete response at 1 month		Outcome 2 (Permanence) complete response at 3 month		Outcome 3 (Efficacy) total response (Complete + partial) at 3 month		Outcome 4 (Tolerance) Adverse effect causing stop drug, minor side effects	
			Combi	Desmo	Combi	Desmo	Combi	Desmo	Combi	Desmo
1	Kazi A, 2020, Pakistan, (12)	n=84, 42/42	13	13	42	36	42	41	Nil,7	Nil/1
2	Ravanshad Y 2017, Iran (13)	n=59 30/29	25	21	26	13	26	13	Nil,20	Nil, 23
3	Almsafer MM 2017, Iraq (14)	n=41 20/21	10,	10	12	12	18	18	Nil , 4	Nil, 2
4	Azhir A, 2008, Iran(15)	n=31 10/21	3	1	7	5	9	16	Nil	Nil
5	Lee T, 2005, Korea, (16)	n=97 48/49 (double dose in desmo)	22	11	21	23	42	45	Nil	2 Withdwal
6	Caione P, 1997, Italy (17)	n= 87 24/63	17	50	17	50	17	50	nil	nil
7	Montaldo P 2011,Italy (18)	n=120 61/59	13	3	13	3	28	10	nil	nil
8	*T Neveus 1999, Sweden(19)	n=33 28/33	13	5	13	5	20	9	nil	nil
9	*E Radvanksha 2006, Denmark (20)	n=60 19/60	19	21	19	21	19	41	nil	nil

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Almusafer MM 2017	+	?	?	?	+	+	+
Azhir A 2008	-	-	-	-	+	+	+
Caione P 1997	-	-	-	-	+	+	?
Kazi A 2020	+	?	+	+	+	+	+
Lee T 2005	+	?	?	-	+	+	?
Montaldo P 2012	+	?	+	+	+	+	+
Neveus T 2001	+	?	?	?	+	+	?
Radvanska E 2006	?	?	-	-	+	+	?
Ravanshad Y 2017	+	?	?	?	+	+	+

Figure 1 : Study characteristics in terms of Risk of Bias Assessment

Discussion :

All included studies had individually shown a better and statistically significant result in favor of combination therapy in their original published results, as well as in the forest plot prepared on analysis of raw data from studies. Most of studies have shown just a marginal favor for combination therapy and are very near to the null line. We used random effect model and Mantel Haenszel statistics for analysis of risk ratio. All included studies have consistently shown the results in favor of combination therapy as depicted in forest plot at confidence interval of 95%. The combined effect diamond also favors combination therapy. It was noticed that the dose of Desmopressin monotherapy

had to be double to reach comparable results almost equivalent to combination therapy, but this high dose is not desirable and chances of side effects especially hyponatremia are higher in such situation, where as combination therapy at therapeutic doses appears to be most successful and easily applicable especially in resource poor settings, without much fear of strict monitoring. The increased response rate may be attributed to covering both groups having predominant polyuria or predominant bladder over activity as both issues are addressed. Good response to combination therapy as compared to desmopressin monotherapy has also been found in retrospective studies done recently in April 2021 by A Gozukucuk.²¹ as well as in past in 2005 by Sajjad A.²² Although these studies were excluded from analysis for being retrospective in nature. It is worthwhile to note that they also mentioned about continued combination therapy for 6 months with no major side effects. Although in our review, on the count of follow up after stoppage of therapy, we did not find enough data to combine the effect size but the observation was that treatment needs to be followed for at least 6 months or more and relapse rate is very high if treatment is stopped earlier. However most of studies which we included either did not go up to 6 months or more or they failed to report clearly what happened after stoppage of therapy. When and how therapy should be stopped or tapered , how long it will take to stop treatment completely remains still unanswered clearly in the world of evidence based medicine. On the count of quick and early response, which is the desired outcome and an incentive for continuation of therapy, combination therapy was favored as measured in Outcome 1 (Forest plot 2). On the count of adverse effects leading to stoppage of therapy as measured in outcome 4 , no such side effect was noted in combination therapy , however it was noted in desmopressin group when double dose (0.8mcg/day was being used). Therefore we can conclude that higher doses are not desirable although they may control the enuresis better as compared to lower usual therapeutic doses. Therefore it appears that combination therapy is better in this sense also and is tolerated better, than higher dose Desmopressin as the need for increasing the dose to get similar results is gone. It is known that excessive use or higher dose of Desmopressin is associated with hyponatremia where as use of combined treatment may reduce the dose of desmopressin and prevent occurrence of clinical or subclinical hyponatremia for similar results.

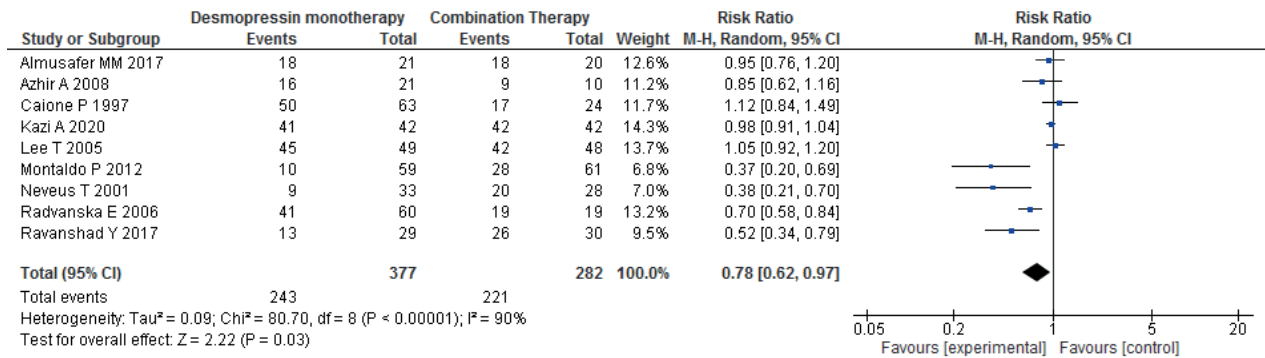


Figure 2 : Forest plot for Out come 3 Efficacy : Combination therapy versus desmopressin monotherapy

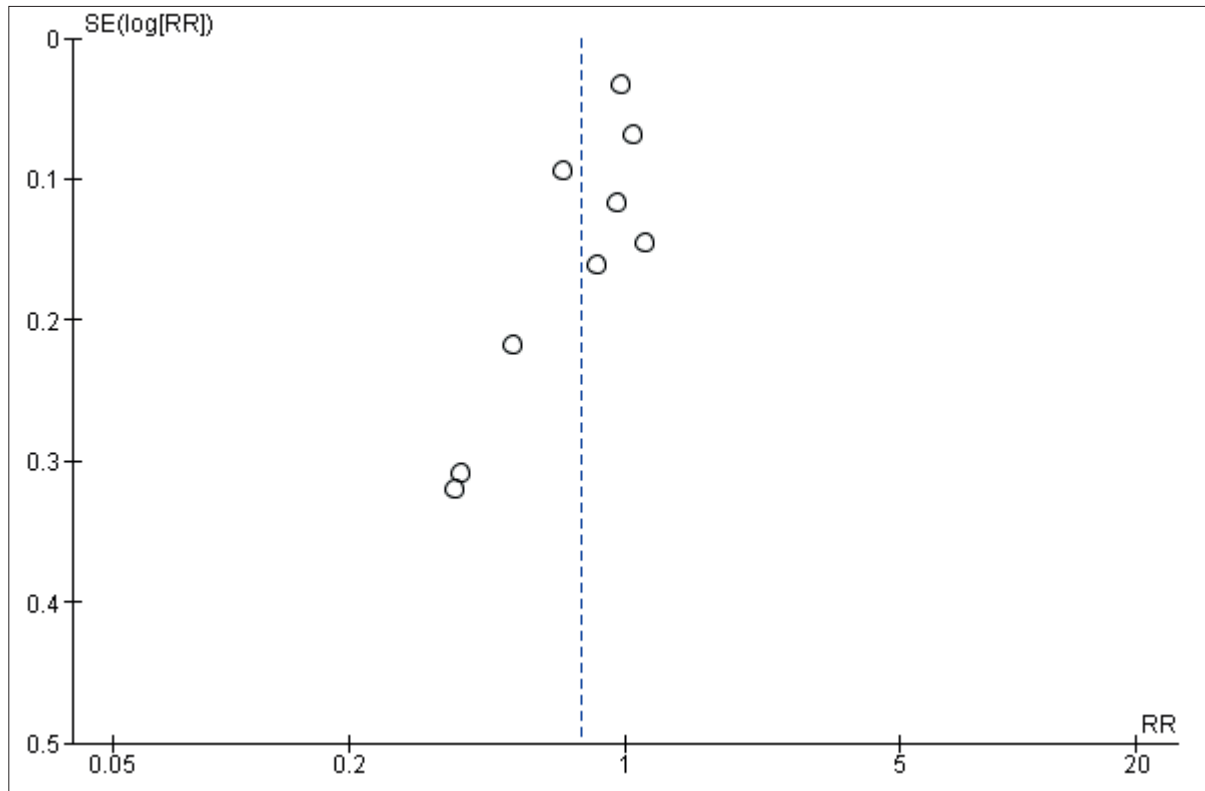


Figure 3 : Funnel plot for Out come 3, Efficacy : Combination therapy versus desmopressin monotherapy

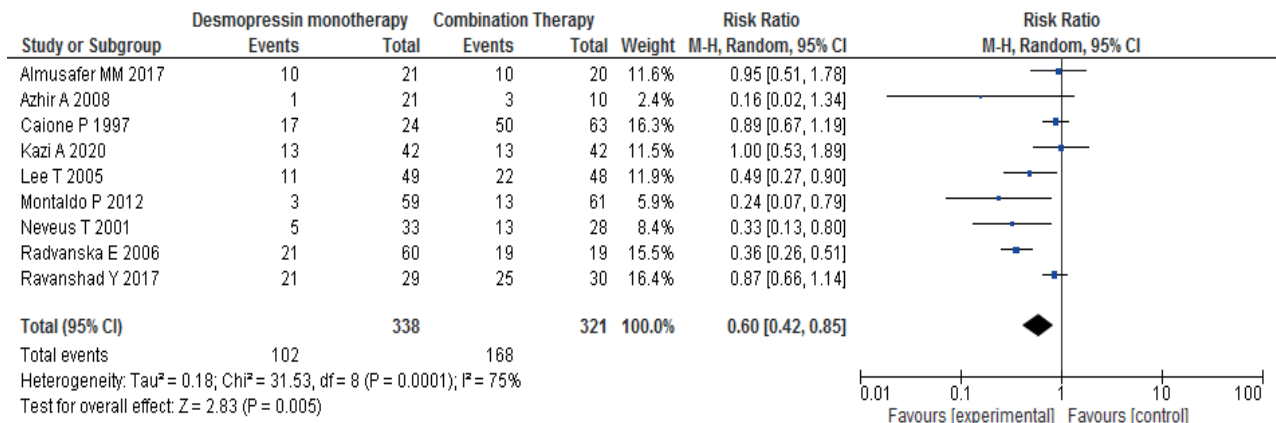


Figure 4 : Forest plot for Out come 1 : Combination therapy versus desmopressin monotherapy

Table 3 : Study characteristics of other comparison groups (Combination versus other monotherapy/ other therapy)

S.no.	Author, Year, location, Reference	Type of patient	study Type	Age group	Efficacy, duration (months)	Entry time	Combination of drug, dose	Number Intervention /Control
Combination versus Oxybutynin								
1	Almsafer MM 2017, Iraq (14)	MNE	RCT con. sampl	6-14	1,3	Begin	(A)20 µm I/N desmopressin + 5 mg Oxybutynin (C) 0.2mg/kg Oxybutynin	n=41 20/18
2	Caione P, 1997, Italy (17)	MNE/ poly	CT	6-24	1,2,5	Begin	30 µm I/N DDAVP spray , 0.2 mg/kg oxybutynin (C) 0.2mg/kg Oxybutynin twice daily	n=114 24/24
Combination versus Imipramine								
1	Lee T, 2005, Korea, (16)	MNE/ Poly both	RCT con. sampl	6-15	1,3,6	begin	(A) 0.1-0.2 mg Desmopressin + 5mg Oxybutynin (D) 25 mg Imipramine	n=96 48/48
2	Boris Chertin 2007, USA (23)	NE	RCT, Stratified sampling	6-11	1,3,12	begin	(A)0.2-0.4 mg Desmopressin + 0.2 mg/kg Oxybutynin TDS (D)25 mg Imipramine alone	n=54 27/27
Combination versus Tolterodine combination								
1	Azafar A,2015 Iran (22)	MNE	CT Open	5-14	1,3	begin	(A)0.2 mg Desmopressin + Oxybutynin (SD) (E)0.2 mg Desmopressin + tolterodine (SD)	n=59 29/30

Table 4: Summary result of other comparison groups (Combination versus other monotherapy/other therapy)

S.no.	Study	Number Exp/ Con	Outcome 1 (Speed) 1 month		Outcome 2 (Permanence) 3 month		Outcome 3 (Efficacy) total response 3 month		Outcome 4 (Tolerance) Adverse effect causing stop drug, minor side effects		Risk Ratio M-H , Random, 95% CI for Outcome 3
			Combi	Oxy	Combi	Oxy	Combi	Oxy	Combi	Oxy	
1	Almsafer 2017	n=41 20/18	10	6	12	9	18	15	nil, 4	nil,4	1.08[0.84,1.39]
2	Caione 1997	n=48 24/24	17	13	17	13	17	13	nil	2	1.31[0.83,2.05]
			Combi	Imipra	Combi	Imipra	Combi	Imipra	Combi	Imipra	
3	Lee 2005	n=96 48/48	22	5	21	16	42	31	nil	2	1.35[1.07,1.71]
4	Boris 2007	n=54 27/27	NA	NA	NA	NA	21	7	NA	NA	3.00[1.54,5.86]
			Combi	Toltero	Combi	Toltero	Combi	Toltero	Combi	Toltero	
5	Azafar 2015	n=59 29/30	21	25	13	26	13	26	NA	NA	0.52[0.34,0.79]

As there was paucity of data in comparison groups with oxybutynin monotherapy and Imipramine monotherapy, the other two commonly used pharmacotherapy, we did not go for network nodal analysis, however the results of analysis on similar

lines are mentioned in table 4. It is clearly understood that combination therapy performed better than Imipramine or oxybutynin both. Imipramine and Oxybutynin alone have already fell out of favor due to either adverse effects or poorer results.

However another promising aspect was that when this combination was compared with another combination of desmopressin and tolterodine, tolterodine outperformed our combination group, opening up a new direction of combination therapy.^{23,24} Desmopressin tolterodine has shown promising results when compared to Desmopressin monotherapy in other studies also^{25,26}. This combination may prove to be a better alternative than the combination being reviewed here²⁷, but it settles for clinicians that combination therapy is a better first line approach, similarly suggested by Korean Children's Continence and Enuresis Society²⁸. Combination therapies with Solifenacin, Propiverine have also shown good results. But more RCT are needed to clearly favor them^{29,30}. Others in pipeline for evaluation are Reboxetine, Atomoxetine and Mirabegron, but data is still very little to comment upon or compare^{31,32}.

Conclusion:

Here we conclude that Combination therapy of Desmopressin and Oxybutynin at usual therapeutic dose is a favorable choice to be applied clinically at the outset without much paraphernalia and delay in start of therapy. However even after combining the studies effect size and evidence is not robust for developed and resourceful countries. There is quite a chance of bias and more studies with good sample size and robust randomization with blinding, need to be conducted globally to support or refute the evidence. But this combination therapy not only appeared to be better than Desmopressin monotherapy but also superior to Imipramine and Oxybutynin monotherapy also.

Amongst the Combination therapy there are chances

that Desmopressin and tolterodine option may be better as compared to desmopressin and oxybutynin option, but the results are from one study only, therefore more studies are needed in this area to gather evidence for practicing clinicians. However the paradigm shift from sequential treatment to combination therapy at the outset appears to be justified.

Recommendations : We recommend that Combination therapy of Desmopressin and Oxybutynin at usual therapeutic dose should be used at outset in resource poor developing countries where pretreatment phase needs to be minimized and compliance is a desired goal without need for many investigations and strict monitoring.

New message from this research : A paradigm shift from sequential treatment to combination therapy at the outset

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Authors Contribution :

Data gathering and idea owner of this study : Dr. Rita Hajela

Study Design : Dr. Rita Hajela, Dr. Rajeev Vinayak, Dr. Hemant Gupta

Data gathering : Dr. Rita Hajela, Dr. Rajeev Vinayak, Dr. Hemant Gupta

Writing and submitting : Dr. Rita Hajela, Dr. Rajeev Vinayak, Dr. Hemant Gupta

Editing and approval of final draft : Dr. Rita Hajela, Dr. Rajeev Vinayak, Dr. Hemant Gupta

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