A systematic review for evidence of efficacy of anticholinergic drugs to treat drooling

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Drooling frequently occurs in children with multiple handicaps; application of anticholinergic drugs is a potential strategy to treat drooling. A computer aided search of original studies concerning the treatment of drooling was carried out. The methodological and statistical integrity of the identified studies were assessed with previously defined criteria. The articles were weighed for their separate contribution to the evidence. The search resulted in 64 reports, of which seven studies passed the screening and were subjected to further assessment and discussion by three referees. Because of the small number of reports and the methodological restriction within the studies, no meta-analysis could be performed. No general conclusion could be made about the efficacy of anticholinergic drugs in treatment of drooling in children with multiple handicaps. There was some evidence that three anticholinergic drugs (benztropine, glycopyrrolate, and benzhexol hydrochloride) are effective in the treatment of drooling, but it could not be concluded that one drug is preferable.

METHODS

Search
Material for the review (articles about relevant studies published before June 2002) was identified by a systematic search in the bibliographic databases of Medline (from 1966), PubMed (from 1966), the Cochrane Library, and Current Contents (from 1996) using the keywords shown in table 1. The keyword “anticholinergic drug” appeared to be inadequate, because studies in the emotional and behavioural development of the individual. The unsightly nature of the drooling and salivary spray when the child talks, sneezes, or coughs can result in a degree of alienation. Patients who are aware of the problem are less likely to interact with other children during normal peer activities. Drooling has been reported to be a significant problem in about 10–37.5% of patients with cerebral palsy.2 4 7

Bachrach and colleagues interviewed parents by means of a questionnaire that included questions regarding drooling. Thirty four per cent indicated it was sometimes a problem, and 16% that it was often a problem. Carers often spend much time in suctioning and cleaning the children's mouths and changing their clothes. Attempts to reduce drooling have included both invasive and non-invasive techniques.11 The latter refers to behavioural techniques, speech therapy, oral sensory and motor training, orthodontic treatment,11 12 anticholinergic drugs,7 13–21 and (intra-ductal) radiation.22 23 Surgical procedures include salivary gland excision,24 salivary duct rerouting,2 25–27 or a combination of these. Chordatympanic neurectomy has been performed to eliminate parasympathetic stimulation to the salivary gland.25 Use of anticholinergic drugs is regarded as a realistic possibility to treat drooling, and many physicians are exploring the effect of these agents together with physiotherapy and speech therapy, as first choice treatment.2 11 13 14 16–20 22–27 In a narrative review of the literature, Nunn28 concluded that “the lack of a scientific approach to many of the studies cited makes it virtually impossible to conclude that any one approach is better than another”.

The objective of this study was to perform a systematic review of the literature, to investigate the efficacy of anticholinergic drugs in the treatment of drooling in children with multiple handicaps.
which the generic name for a specific drug was used would be excluded. The keywords were expanded by using the “explode function” present in Medline.

References from the retrieved articles were checked. The retrieved articles were screened by title. If any uncertainty remained, printouts of the abstracts were checked.

Only patient related studies aimed at the treatment of drooling with anticholinergic drugs in multiply handicapped children and published in the English, German, Dutch, or French languages were included. Letters, abstracts, and “published presentations” were excluded. Table 2 provides the definitions and the exact inclusion and exclusion criteria for the articles. Three referees (PJ, PvT, and JvL) independently analysed all selected studies.

The publications were blinded with respect to author, source, and results. Subsequently the level of methodological quality was assessed. Studies that passed the preliminary screening were subjected to a systematic review using a checklist with previously defined methodological criteria. The checklist (table 3) was constructed according to a system originally developed for the evaluation of randomised controlled clinical trials (RCTs).13–16

Each criterion for internal validity (V1–V7), external validity (V8–V15), and the method of data presentation (D1–D5) was assessed and scored with a three level system: [3], sufficient; [2], moderate; [1], insufficient. If a choice had to be made between sub-items, only one of these could be filled in and the other sub-item was scored [0].

This system implies a maximum sum score of 60 points for the 20 items on the checklist. However, some items were not applicable [NA] in view of the specific study design. In such a case the maximum sum score decreased accordingly.

| Table 1 | The applied keywords for the literature search |
| Groups | Keywords | Groups | Keywords |
| Pharmacological preparations | Symptoms | Treatment | Population |
| 1. Anticholinergic drug | Drooling | Treatment | Child |
| 2. Anticholinergic drugs | Drool* | Treatments | Children |
| 3. Anticholinergic drug* | Hypersalivation | Treatment* | Child* |
| 4. Anticholinergic medication | Hyper* | Intervention | Infant |
| 5. Anticholinergic treatment | Dribbling | Interventions | Infants |
| 6. Anticholinergic treatments | Drib* | Intervention* | Infant* |
| 7. Anticholinergic treatment* | Sialorrhea | Management | Preschool child |
| 8. Cholinergic blocking | Sial* | Management* | Preschool children |
| 9. Cholinergic blockings | Phyalism | Therapy | Preschool child* |
| 10. Cholinergic blocking* | Phyal* | Therapy* | Adolescence |
| 11. Cholinergic antagonist | Siala | Pediatric patient |
| 12. Cholinergic antagonists | Sial* | Pediatric patients |
| 13. Cholinergic antagonist* | High salivary secretion | Pediatric patient* |
| 14. Cholineesterase inhibitor | High salivary secretions | Juvenile |
| 15. Cholineesterase inhibitors | Salivation | Juveniles |
| 16. Cholineesterase inhibitor* | Salivary flow | Juvenil* |
| 17. Parasympaticolitics | | | |
| 18. Parasympaticolitics | | | |
| 19. Anti?muscarinic | | | |
| 20. Scopolamine | | | |
| 21. Scopoderm TTS | | | |
| 22. Hyozone | | | |
| 23. N-methylscopolamine | | | |
| 24. Butylochloromium bromide | | | |
| 25. Benztropine | | | |
| 26. Glycopyrrolate | | | |
| 27. Atrone | | | |
| 28. Pyrilotamine | | | |
| 29. Benhexylhydrochloride | | | |
| 30. Antisialorrheic | | | |

Table 2 | Definitions and criteria for selection and inclusion of articles in the study |
| Definitions | |
| • Child: a person up to the age of 18. |
| • Drooling: “the unintentional loss of saliva from the oral cavity due to pyramidal or extrapyramidal impairment”. |

Criteria for inclusion of selected articles |
| • The study is patient related and aimed at the treatment of drooling with drugs. |
| • The study has been performed as a clinical trial, cohort study, case series, case-references, or case-control study. |
| • The study population or relevant subgroup primarily concerns children of preschool and school age. |
| • The treatment of drooling has been evaluated with descriptions of the population (diagnosis and an indication of impairment and disability), the intervention, and the outcome measure. |
| • Published in the English, German, Dutch, or French languages. |

Criteria for exclusion of selected articles |
| • Articles written in other languages that only provided an abstract in English. |
| • Letters, abstracts, and published presentations without acceptable description of methodology, population, and results. |
| • Narrative reviews. |
Internal validity

Randomisation (V1) is a critical issue. The description of how randomisation was achieved had to be made clear. It was not possible to verify whether the randomisation procedure was properly executed as this is hardly ever mentioned in published work.

The homogeneity (V2) of the study population has been assessed. The item on homogeneity is subdivided into two sub-items (V2a and V2b). These items evaluate the comparability of subjects within the population with respect to the underlying mechanism of drooling; it ought to be reflected in homogeneity for diagnosis and the resultant motor impairment. This item also investigates the homogeneity of the population under study with respect to confounding factors at entry to the study (age, stage of the disease, co-morbidity, and co-medication) that could influence salivary flow. In particular, concurrent use of anticholinergic medication as well as caries, and periodontologic disturbances is of importance. A [3] was assigned if the population was well documented. In case incomplete data had been given a [2] was scored. In cases where there was insufficient information to determine the degree of homogeneity, a [1] was scored. A V2a score of [2] or [3] satisfied the minimum requirements for homogeneity. Consequently subgroup analysis was not needed for this study and item V2b was scored as [0]. If V2a had a score of [1], subgroup analysis had to be performed. In case subgroup analysis had been carried out, the score for item V2a was transformed to [0].

Adherence to therapy (V3) had to be measured and indicated in the description of the study. Control for relevant intervention at entry and during the trial (V4) had to be described and to be controlled (that is, surgery in the oral cavity, behavioural therapy, and the application of medication aimed at reducing drooling).

A quantitative indication of the severity of drooling was always required. The accuracy of the applied severity or frequency scoring system was evaluated (V5). A quantitative score or ratio scale provided in absolute numbers (for example, ml/min) was judged sufficient [3]. Semiquantitative scores that used an ordinal scale such as the "Teacher Drooling Scale" were classified as moderate [2]. The use of dichotomous scales was considered to be insufficient [1]. Outcome measurements had to be repeated at fixed intervals during a relevant period after start of the intervention (V6).

Randomised clinical trials had to meet the intention to treat principle (V7).

External validity

The description of inclusion and exclusion criteria for subjects (V8) in a study was considered to be essential. A thorough description of the planned therapy (V9) was obligatory. This item scored sufficient if a description was given. Co-interventions during the trial (V10) had to be described and the relevance with respect to the therapy had to be mentioned. The outcome measures such as ratio scales or the results of ordinary scales had to be described in the text (V11). In case the description was unclear or provided no meaningful information, this item was regarded as insufficient.

The reasons for "lost to follow up" (V12) had to be given, and these cases needed to be managed adequately. This item also scored positive in case there were no drop outs during the study or if the description of the drop outs contained convincing arguments. The absolute number or the percentage of subjects "lost to follow up" (V13) needed to be mentioned. Based on the information provided, it was demanded that the percentage of "lost to follow up" could be calculated.

The follow up period had to be long enough (V14) to determine the usefulness of the anticholinergic drug treatment and possible side effects. This period was determined to be a minimum period of eight weeks since it could be expected that side effects would be clear by that time. Side effects of the therapy (V15) were regarded as a critical success factor. This criterion tested whether there had been sufficient control for side effects.

Data presentation

The number of patients was judged in relation to the study design (D1). Outcome measurements had to be adequately reported with quantitative measures (absolute numbers or relative difference scores), and presentation of the mean (D2) and standard deviation (D3).
The planned statistical analysis had to be described clearly in relation to the proposed research design (D4), and the article had to provide evidence the statistical analysis had indeed been conducted (D5).

RESULTS OF THE LITERATURE SEARCH

The primary search resulted in 64 articles. Of these, 36 were excluded based on the contents of the abstract, and 30 articles appeared to be irrelevant in relation to the research questions of this review. Three RCTs and one cohort study; these duplicates were removed. One Japanese article was excluded, as were two articles concerning case reports. One article was recognised as a narrative review. The remaining 28 articles were read completely. Seventeen articles without abstracts were rejected from the study because they were not relevant to the research questions. One article was recognised as a narrative review and was excluded. Two articles did not concern children or problems related to CP. One study had a retrospective design and was excluded. Screening of the references of all articles did not bring up new articles.

Sixty four articles were retrieved in the primary search, from which seven articles could be selected for further investigation.

The methodological quality of the seven selected articles was determined (table 4). Three studies were RCTs, three were cohort studies, and one had an experimental design.

In this review one RCT, one study with a classical Virchow design, and one cohort study were judged as methodologically adequate in relation to the study design that was used. Two RCTs and two cohort studies did not meet the proposed methodological criteria. In order to provide a complete overview of the available literature, these articles are also listed in table 4.

For the methodological quality of the selected RCTs the internal validity (table 4) was regarded as the most critical aspect, in particular homogeneity (V2), Randomisation (V1), the “intention to treat analysis” (V7), adherence to treatment (V3), and the method of outcome measure (V5) were weighed as equally essential. Randomisation and intention to treat are items that are not applicable for cohort studies. To be qualified as an article with good internal validity, the studies had to satisfy the above mentioned criteria of internal validity with a minimum score of 12 points (out of 21) for RCTs or 8 points (out of 15) for cohort studies. Table 4 lists the outcomes of the items on internal validity, external validity, and data presentation.

Three referees analysed the selected articles. The scores for the methodological and statistical items were scored on prepared lists. Consensus about particular items was acquired by a thorough discussion. It has not been necessary to consult another referee.

DESCRIPTION OF THE INCLUDED STUDIES

In this section the separate articles are described with respect to the methodological quality and the clinical relevance of the presented information.

Camp-Bruno et al investigated the effect of benztropine for the treatment of drooling in 27 subjects in a placebo controlled RCT. The scoring method of the severity and frequency of drooling was outlined in detail. Homogeneity of the population was rated insufficient because there was no correction for age (in the literature an influence of age until puberty on salivary flow has been described). Subgroup analysis was not performed. Control for adherence to therapy was considered sufficient. The criterion of the “intention to treat” principle was not satisfied. Of the 27 patients, seven were later drop outs. In the opinion of the reviewers a percentage of 30% drop outs was too large. Adverse effects of three patients were described; data for the other four were missing. The adverse effects were scored on an ordinal scale. Unfortunately the outcomes of the measurements were not presented. The internal validity was too large. Adverse effects of three patients were described; data for the other four were missing. The adverse effects were scored on an ordinal scale.
validity of the study was good: 85.7% (18/21)—that is, 18 out of a maximum of 21 points), although the “intention to treat” principal was not satisfied. The external validity was good: 83.3% (20/24), as was the way in which the data were presented: 100% (15/15). In conclusion, this study could be used for the evidence synthesis.

The study by Camp-Bruno shows that in principal benztropine can have a positive effect on drooling. On the other hand, one cannot make a statement about the average effect of the drug. During the study the population with 27 subjects was too small to compensate for a drop out percentage of almost 30%. Three of the seven drop outs were certainly related to the treatment. With the results presented, the question of whether the treatment and its adverse effects cannot be made because the study has a follow up period of a few weeks.

Mier et al. performed a double blind, crossover study to evaluate the efficacy and dose range of glycopyrrolate to treat drooling. Thirty nine children were enrolled. Randomisation was not described and no information was given about the inclusion and exclusion criteria of the subjects. There was insufficient homogeneity in the population because there was no correction for age. Sufficient information was given about the mechanism of drooling, other medical conditions, and adherence to therapy. The criterion of the “intention to treat” principle was not satisfied. The scoring method of the severity and frequency of drooling was outlined in detail. Two dosage regimes for glycopyrrolate were used and sufficiently described. Results were presented in a clear way and sufficient statistical information was provided. Referring to the chosen design, the number of patients included is enough to require adequate statistical power. The number of drop outs (31%) is not acceptable. This, together with the fact that the intention to treat principle was not satisfied, seriously reduce the methodological value of the study, in particular because the drop outs appeared to be selectively related to the medication. The score on internal validity was low to moderate: 52.3%, because of insufficient description of randomisation and the study population. External validity scored 83.3% (20/24) and data presentation 100% (15/15). Because of the score on internal validity, this study could be used in the evidence synthesis to support primary evidence.

The authors conclude that children tolerating glycopyrrolate will show “marked improvement in drooling” at individual doses. Dosage guidelines are provided. In 20% of the cases, adverse effects necessitated withdrawal of glycopyrrolate.

Lewis et al. investigated the effect on drooling of a transdermal application of scopolamine, in a placebo controlled RCT with a crossover design. A two week period of scopolamine was plotted against the same duration of placebo treatment. The homogeneity of the population was insufficient and no adequate subgroup analysis was carried out. The adherence to therapy was not described and the method of measurements insufficiency described. A five level scale was used in which the amount of present drooling during therapy was compared to the usual situation for the particular patient. In this respect the patient was supposed to serve as his or her own control. The method was regarded as being insufficient because it was unclear how many people finally observed a particular child and in which way data were calculated. The “intention to treat” principal was not satisfied. Side effects were well documented. The method of statistical analysis was described in relation to the design used, but the analysis itself was not presented in sufficient detail. For example, no means and standard deviations could be calculated.

Internal validity of this study was moderate: 57.1% (12/21). External validity scored 79.2% (19/24) and data presentation 60% (9/15). The article could not be used in the evidence synthesis because of the low internal validity in combination with the way data were presented.

The authors present a good overview of the possible side effects of scopolamine: pupil dilatation, dizziness, pruritus around the patch, and increased mouthing behaviours. One child experienced deterioration of a pre-existing refractory seizure disorder.

Owen and Stern investigated the effect of benztrapine on salivary flow using the classical Virchow design: a–b–a–b. Three patients were enrolled in this study. Salivary flow was scored using an ordinal scale. A baseline period was introduced followed by a period of optimal dose finding. After a washout period the patient received medication or placebo (within subject design). Using this design, follow up was not required because it was not relevant in relation to the research question. The methodological quality of the study was correct. The a–b–a–b design in this case could only answer the question whether the salivary glands react to the application of benztrapine. From the results presented, it can be concluded that the inter-individual variation was rather large. A general conclusion for a population could not be drawn because of the small number of patients. The study does not permit a judgement as to whether benztrapine is a useful therapy in the treatment of drooling in children with CP, in general. There was insufficient homogeneity in the population because of the great variation in age of the three participants. Subgroup analysis was not conducted although the diagnosis and potential confounders were mentioned, but in the discussion of the results these data were not related to a specific patient. Because of the chosen design, it was methodologically inadequate not to mention co-interventions. The performance of statistical analysis was insufficient since no information was given as to whether analysis was actually done. No results were reported. The internal validity score was moderate: 57.1% (12/21). The score on external validity was moderate: 66.6% (16/24) and more attention should have been paid to the data presentation: 60% (9/15). Because of the objective and the chosen research design this study could only be used as additional information to support the evidence.

The study by Owen and Stern indicates that the salivary glands would react to benztrapine with a positive effect on salivary flow. With the limited subjects included and the chosen research design, no conclusion can be made about the average effect of the drug in a certain population.

Reddihough et al. studied the effect of benzhexol hydrochloride (Artane) on drooling. During three months, 20 children, 3–12 years of age were treated. The outcome measure was described in detail and well standardised. The authors provided the reader with a fair indication of how drooling was defined during the observations in a well documented homogeneous population. The wide spread in age of the participating subjects could be criticised. Control for the adherence to therapy and co-intervention was insufficient. Inclusion and exclusion criteria were sufficiently described, as was the intervention. The outcome measures were unfortunately listed in the text as a description for the population as a whole. From the presented results table, it was not clear which data belonged to a particular patient. This might have been of importance with respect to the differences in age. Results were presented as percentages of the median score of drooling before and during treatment. Statistical procedures were clearly presented. The score on internal validity was moderate: 66.6% (10/15); external validity was good: 75% (18/24). Data presentation scored 100% (15/15). The study by Reddihough et al., a cohort study, only provides additional information to support the evidence. In the evidence synthesis this study could be used as secondary evidence.

Following good clinical practice the problem of drooling is outlined together with the remark that “salivary flow is profuse in infancy, but decreases rapidly up to five years and then more gradually to puberty”. The article gives additional information about the application of benzhexol hydrochloride and description of how the optimal dosage was achieved. No
relation was found between the dosage and the age of the child. Drooling decreased in 17 of 20 subjects. Because the study was of reasonable methodological quality, two conclusions are likely: (a) benzhexol hydrochloride has a good effect on drooling, although the average effect remains unclear; and (b) the optimal dosage varies from 2×2 mg up to 2×3 mg daily.

Blasco and Stansbury\(^1\) investigated the effect of glycopyrrolate as a treatment for drooling in 40 children. This was a cohort study that did not satisfy the minimal requirements for internal validity. The data about the homogeneity of the population were incomplete; no information was provided about potential confounding factors such as age, stage of the disease, co-morbidity, inflammation, and caries. The use of medication was made explicit and half of the population appeared to use a variety of drugs, but no appropriate information was given as to whether these drugs could influence salivary flow. Adherence to therapy was not indicated, and the method of outcome measures was graded as insufficient since a dichotomous scale was used. All items for external validity but one were scored positive; unfortunately the outcome measures were not listed in the text. In the data presentation baseline measures were not mentioned. Internal validity scored low at 40% (6/15), external validity 91.6% (22/24), and data presentation 45.6% (7/15). Based on the data set presented in the article, together with the scores on internal validity, no statement could be made about the efficacy of glycopyrrolate on drooling.

Although this study cannot be used in the evidence synthesis, the information provided is of clinical importance. A short overview of the problem of drooling and the treatment possibilities were given. The use of anticholinergic drugs and in particular the dosages of glycopyrrolate were presented. This is in line with the opening sentence of the article in which the author stated that the objective of the study was to outline “the use of glycopyrrolate in the control of drooling in children and young adults with CP and related neurodevelopmental disabilities”.

In the study by Stern\(^1\) the effect of glycopyrrolate to treat drooling was investigated in a population of 24 subjects. Although the mean age of the participants is given, it is not possible to determine whether more than 50% of the population is under the age of 18. The outcome measures used have limitations. Parents were asked to complete a questionnaire “some time after the end of the trial” in order to assess the effect of glycopyrrolate. This uncertain time interval violated the quality of internal validity. The authors admit that the way in which the questionnaires were completed is open to discussion and criticism. Adherence to therapy was not described. The items on the inclusion and exclusion criteria, homogeneity, and the performed intervention were satisfied. The number lost to follow up was not indicated. The measurements before the start of the therapy were not listed in the text, nor were the post treatment results given per patient. Insufficient insight was acquired in the effect of the intervention with glycopyrrolate. Information about statistical analyses provided in the text was inadequate. Internal validity scored moderate at 66% (10/15), external validity: 75% (18/24), and data presentation 73.3% (11/15). As a case series the study could not be taken into account for “evidence synthesis”.

From a clinical point of view the authors provide a good overview of the mechanism of drooling in general and the treatment possibilities, even though this was not the purpose of the article.

EVIDENCE SYNTHESIS AND DISCUSSION

Evidens synthesis

RCTs can be considered to give primary evidence, whereas cohort studies, referred to as pre-experimental design, can only provide additional information to support the outcome of the RCTs. We performed an in depth review of the medical literature in order to do a meta-analysis. Unfortunately only seven studies could be identified. In our review, articles subjected to a methodological assessment can be weighed for their contribution to the “evidence” that the application of anticholinergic drugs is indeed effective in the treatment of drooling. For the methodological quality of the selected RCTs the internal validity (table 4) was regarded as the most critical aspect.

The RCT by Camp-Bruno and colleagues\(^1\) acquired sufficient points on internal validity, even though the item “the intention to treat” was graded as insufficient, but the methodological assessment scores of [3] for randomisation (V1) and homogeneity (V2a) compensated for this. The other RCTs\(^1\) did not satisfy the criteria for internal validity. Mier et al did not describe randomisation and inclusion criteria and consequently scored moderate on internal validity. In conclusion, one RCT can be weighed as a “high grade evidence”\(^2\) study, one as “moderate grade evidence”\(^2\), and one as a “low grade evidence”\(^2\) study.\(^1\) In relation to the objective of this study, the RCT by Camp-Bruno et al contributes most to the evidence. The experimental study with the Virchow design\(^4\) scored 12 of 12 possible points on internal validity. Although not an RCT, this study was judged to provide additional information to the primary evidence.

The cohort study by Reddihough and colleagues\(^1\) was considered to be a “moderate informative” study. The other two cohort studies by Blasco and Stansbury\(^1\) and Stern\(^1\) were regarded as “less informative”.

DISCUSSION

For many clinicians, the application of anticholinergic drugs is regarded as a realistic possibility to treat drooling and is the first choice therapy. This systematic review investigated the literature for evidence of the effectiveness of anticholinergic drugs in the treatment of drooling in children with multiple handicaps. An overall problem in the studies found is that no single method of measurement of salivary flow and outcome presentation is available. We endorse the plea for the development of a “golden standard”\(^1\). Another problem is that in the selected studies, no drug has been repeatedly evaluated. As an outcome of our study no statement can be made about the long term effects of anticholinergic drug therapy because none of the studies describe a follow up period greater than a few weeks. Adverse effects were reported in all studies. Only one study provided precise information as to what extent side effects necessitate termination of therapy.\(^1\) Frequently reported side effects are irritability, restlessness and overactivity, disorientation, marked pupil dilatation, and constipation. Other, less frequently reported side effects are insomnia, headaches, epileptic seizures, vomiting, difficulty in initiating micturition, dry mouth and lips, “picking and grasping” movements, and epistaxis.

From the articles by Camp-Bruno et al and Owen and Stern, it can be concluded that a daily dosage of 3 mg to approximately 3.8 mg benztropine should be effective in the treatment of drooling. This implies that benztropine could be used in the treatment of drooling, although adverse effects should be thoroughly controlled and no indication of long term effects can be given. Reddihough et al provided additional information to support the evidence of the effectiveness of anticholinergic drugs. A significant reduction in the mean score for drooling was found with a dosage of benzhexol hydrochloride varying from 2×2 mg up to 2×3 mg daily. Mier et al provided support for the primary evidence of the efficacy of anticholinergic drugs. They conclude a marked reduction of drooling in cases where glycopyrrolate was tolerated.
CONCLUSION
The objective of this study was to investigate the efficacy of anticholinergic drugs to treat drooling in children with multi-
ple handicaps. We performed an in depth systematic review of the medical literature in order to do a meta-analysis. Unfortu-
nately only seven studies could be identified. Because of the methodological drawbacks within the studies, no general
conclusion can be made about the efficacy or average effect of anticholinergic drugs to treat drooling in children with multi-
ple handicaps. Future uniformity in measurements can help the interpretation of outcomes. Further research in larger
populations with a longer follow up period should be encour-
gaged. Based on our study there is some evidence that at least
three anticholinergic drugs (benztropine, glycopyrrolate, and
benzhexol hydrochloride) are effective in the treatment of
drooling, but it cannot be concluded that one anticholinergic
drug is preferable above the other. Because of the small
number of reports and the methodological restriction within
the studies, no meta-analysis could be performed.

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