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Systematic review of cholinergic drugs for neuroleptic-induced tardive dyskinesia: a meta-analysis of randomized controlled trials

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Abstract

The authors evaluated the efficacy of cholinergic drugs in the treatment of neuroleptic-induced tardive dyskinesia (TD) by a systematic review of the literature on the following agents: choline, lecithin, physostigmine, tacrine, 7-methoxyacridine, ipidacrine, galantamine, donepezil, rivastigmine, eptastigmine, metrifonate, arecoline, RS 86, xanomeline, cevimeline, deanol, and meclofenoxate. All relevant randomized controlled trials, without any language or year limitations, were obtained from the Cochrane Schizophrenia Group's Register of Trials. Trials were classified according to their methodological quality. For binary and continuous data, relative risks (RR) and weighted or standardized mean differences (SMD) were calculated, respectively. Eleven trials with a total of 261 randomized patients were included in the meta-analysis. Cholinergic drugs showed a minor trend for improvement of tardive dyskinesia symptoms, but results were not statistically significant (RR 0.84, 95% confidence interval (CI) 0.68 to 1.04, p=0.11). Despite an extensive search of the literature, eligible data for the meta-analysis were few and no results reached statistical significance. In conclusion, we found no evidence to support administration of the old cholinergic agents lecithin, deanol, and meclofenoxate to patients with tardive dyskinesia. In addition, two trials were found on novel cholinergic Alzheimer drugs in tardive dyskinesia, one of which was ongoing. Further investigation of the clinical effects of novel cholinergic agents in tardive dyskinesia is warranted.

Keywords: Cholinergic agents; Drug-induced; Dyskinesia; Meta-analysis; Treatment outcome

1. Introduction

The introduction of cholinergic drugs for treatment of Alzheimer's disease and the persisting lack of effective pharmacologic means to treat tardive dyskinesia (TD) makes it timely to systematically revisit previous studies on the efficacy of cholinergic agents for TD.

Systematic reviews have been developed to support evidence-based decision-making in medicine as well as in other sciences. When appropriate, meta-analysis is conducted to pool the results of reviewed studies (Petticrew, 2001). Systematic reviews aim to avoid biases by extensive and systematic literature searches and by using teams of researchers to select and assess the methodological quality of trials (Sterne et al., 2001). For example, inadequate allocation of participants into treatment groups

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; CGI, Clinical Global Impression; CI, confidence interval; GUR, Global Usefulness Rating; RR, relative risk; SMD, standardized mean difference; TD, tardive dyskinesia; TDRS, Tardive Dyskinesia Rating Scale; WMD, weighted mean difference.

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(Schulz and Grimes, 2002a) and shortcomings in allocation concealment (Schulz and Grimes, 2002b) are associated with biases, and therefore, these aspects are inspected carefully.

TD is a serious and disabling motor adverse effect of antipsychotic treatment. Despite development of antipsychotics with a lower risk of causing this condition, TD remains a problem among many patients, especially those to whom second-generation antipsychotics are unavailable.

The exact mechanisms of the pathogenesis of TD are unknown. Several preclinical models, one of them being the dopamine receptor hypersensitivity hypothesis, have been developed to explain the underlying pathophysiology, but none has provided an unequivocal explanation (Casey, 2000). An imbalance between the activity of dopaminergic and cholinergic systems in the basal ganglia has been proposed (Klawans and Rubovits, 1974; Gerlach et al., 1974). Evidence suggests that striatal cholinergic neurons (Miller and Chouinard, 1993), as well as complex neuronal interactions involving several neuronal systems [e.g. glutamate and gammaaminobutyric acid (GABA)-related transmission] contribute to manifestation of this motor disorder (Andreassen and Jorgensen, 2000; Rascol and Fabre, 2001). Research further suggests structural changes in cell morphology (Harrison, 1999), and neurotoxic and neurodegenerative processes (Mitchell et al., 2002), possibly caused by glutamate-mediated excitotoxicity (Andreassen et al., 2001), and oxidative stress (Maurer and Volz, 2001), as contributing factors in the pathogenesis of TD. A recent study shows reduction of cholinergic neurons in specific subregions of the striatum and nucleus accumbens, critical in the regulation of oral movements, after long-term treatment with haloperidol in rodents (Grimm et al., 2001). These findings may support previous hypotheses of alterations in striatal cholinergic neurons as a pathophysiological basis for TD.

A theoretical framework thus exists for the use of cholinergic agents in treating TD. In the 1970s and 1980s, physostigmine, choline, and lecithin were used experimentally to treat TD. Choline and lecithin were thought to act as precursors for acetylcholine, exerting their action through enhanced acetylcholine synthesis (Wurtman and Growdon, 1978). Deanol and meclofenoxate (centrophenoxine), an agent related to deanol, were investigated in TD for their proposed cholinomimetic actions (Casey and Denney, 1975; Izumi et al., 1986). During the last decade, many new cholinergic compounds, predominantly acetylcholinesterase inhibitors, have emerged for the treatment of Alzheimer's disease (Peskind, 1998; Schneider, 1998; Sramek and Cutler, 1999). These agents may also offer a treatment alternative for TD (Caroff et al., 2001). We therefore found it appropriate to evaluate the cumulative evidence for efficacy of cholinergic drugs in treating TD using the rigorous systematic review technique.

2. Methods

2.1. Inclusion criteria

All relevant randomized placebo-controlled double-blind trials investigating the effect of cholinergic agents on TD symptoms were considered in this review. Cholinergic drugs were limited to those exerting an excitatory action on central cholinergic transmission. We included acetylcholine precursors (choline, lecithin), acetylcholinesterase inhibitors (physostigmine, tacrine, 7-methoxyacridine, ipidacrine, galantamine, donepezil, rivastigmine, eptastigmine, metrifonate), central muscarinic agonists (arecoline, RS 86, xanomeline, cevimeline), and the cholinomimetic agents deanol and meclofenoxate. Putative cholinergic agents displaying predominantly other modes of action (e.g. neuroprotective properties) were not included to avoid contamination of effects by noncholinergic mechanisms.

In addition, trials had to fulfill the following predefined criteria in order to be considered: Participants had to have developed TD during antipsychotic treatment (diagnosed by any criteria at trial baseline and on at least one other occasion), and participants' doses of antipsychotic medication had to have been stable for 1 month or more prior to the trial and during the trial, as changes in antipsychotic medication affect tardive dyskinesia symptoms.

2.2. Literature search strategy

An electronic search of the Cochrane Schizophrenia Group's Register of Trials was performed with a search string reported elsewhere (Tammenmaa et al., 2002). The database is publicly available at http://psitri.stakes.fi. No year or language limits were used. The Cochrane Schizophrenia Group undertakes searches of a number of databases and conference proceedings for all trials relating to schizophrenia or chronic/serious mental illnesses as well as the adverse effects and syndromes related to the management of these illnesses, including tardive dyskinesia (Adams et al., 2002). Regular searches of Biological Abstracts, CINAHL, the Cochrane Library CENTRAL, EMBASE, MEDLINE, RUSSMED, LILACS, PSYNDEX, and PsycLIT are conducted, and relevant citations are added to the Cochrane Schizophrenia Group's register. We also inspected reference lists of all identified trials for additional trials and contacted first authors of trials to obtain more information on particular aspects of trials and possible unpublished trials.

2.3. Quality assessment and data extraction

Two reviewers (IT, ES) independently graded allocation concealment according to the predefined criteria of the Cochrane Collaboration Handbook (Clarke and Oxman, 2002) into three classes of quality. Classes A, B, and C included trials with a low, moderate, and high risk of bias, respectively. Only trials graded A or B were included in the

meta-analysis. Two reviewers (IT, KW) extracted data from the included papers. Disagreements were resolved by discussion.

2.4. Statistical analysis

Dichotomous (binary) data from trials were pooled using the Mantel–Haenszel method (Mantel and Haenszel, 1959) to calculate relative risks (RR) and 95% confidence intervals (CI). Heterogeneity between trials was estimated by visually inspecting the graphs, by the statistic I^2 measuring the extent of inconsistency among results, and by using the chi-square heterogeneity test (χ^2). A significance level of $p>0.10$ was predefined as an indication of homogeneous data, and these data were pooled using the fixed effect model. In the case of heterogeneous data, the reasons underlying heterogeneity in trial outcome were explored. A random effects model was used if pooling was judged to be appropriate despite heterogeneity (DerSimonian and Laird, 1986).

When RR equals one, no difference in the efficacy of intervention is present between treatment-allocated and placebo-allocated patients. RR of less than one indicates a beneficial effect for treatment-group patients. In addition, overall efficacy (z) of outcomes was estimated by dividing the effect size estimate by its standard error. Two-tailed statistical significance (p) of z-values is presented.

For continuous data outcomes, a weighted mean difference (WMD) with 95% CI was calculated using reciprocal variance weighting and a fixed effect model. Again, a random effects model was used if there was significant heterogeneity in the results of trials. Standardized mean difference (SMD) was used to enable pooling of data of comparable outcomes in which different rating scales were used in different trials. When possible, continuous outcomes of rating scales were transformed into binary outcomes. This was done using cut-off levels of 50% improvement, any improvement, or any worsening of symptoms. For calculating statistical values, Review Manager (RevMan) 4.1.1 software (The Cochrane Collaboration, 2000) was used. A significance level of $p=0.05$ was set.

A wide range of scales of varying quality have been used to measure TD symptoms. Rating scales which have not been validated (standardized) are more likely to report statistically significant findings than those which are validated (Marshall et al., 2000). Continuous data were extracted only from trials which used validated global or TD rating scales (Cunningham Owens, 1999) in outcome assessment. For trials that had not used standardized rating scales, continuous data from individual patients were transformed into binary outcomes of any improvement or any worsening of symptoms, respectively, since binary data are a cruder estimate of treatment effect.

For clinical continuous outcomes, a risk exists of the data not being normally distributed. To avoid use of parametric tests on nonparametric data, a simple test was used to determine whether data were skewed. When the standard deviation is multiplied by two, the product should be less than the mean, otherwise the mean does not represent the center of the distribution for values on a scale starting at zero (Altman and Bland, 1996). When a scale starts from a positive number, e.g. the Rockland (Simpson) Tardive Dyskinesia Rating Scale which starts at 34, the rule can be applied as follows: $2SD<(S_m-S_{min})$ must be true for nonskewed data, where S_m is the mean score of the data and S_{min} is the minimum score on the scale.

To avoid inclusion of carry-over effects (Sibbald and Roberts, 1998), data after a crossover of patients were not used. Data were solely extracted from the endpoint of the first segment of crossover trials. Potential publication bias was evaluated visually by inspecting funnel graphs (Egger et al., 1997).

Trial-dependent factors were expected to be a source of variation in the results of different trials and to possibly cause significant heterogeneity of the data being pooled. The following factors were defined a priori: (1) drug used in trial, and (2) length of treatment. In the graphical presentation, trials were divided into predefined subgroups according to pharmacological agent and length of treatment, using a cut-off point of 6 weeks to define short-term and long-term treatment in the latter. Statistical values of subgroups were investigated. However, data were ultimately pooled across trials to calculate total RR or WMD for outcomes of interest. Where possible, all data were analyzed by the intention-to-treat principle.

2.5. Outcomes

The primary outcomes of interest were assessor-rated changes in TD symptoms and whether these reached clinical significance. Secondary outcomes of interest were deaths, leaving the study early, changes in mental state (exacerbation of psychotic symptoms), adverse effects, level of functioning, quality of life, and self-assessment of change in dyskinetic symptoms. In the included trials, TD symptoms were measured by the Abnormal Involuntary Movement Scale (AIMS), (Pharmacology Research Branch, National Institute of Mental Health, 1976a) the Rockland (Simpson) Tardive Dyskinesia Rating Scale (TDRS) (Simpson et al., 1979), the Clinical Global Impression (CGI) (Pharmacology Research Branch, National Institute of Mental Health, 1976b), or local scales. In addition, Global Usefulness Rating (GUR), a categorical rating instrument used in Japan that combines an evaluation of treatment effect and adverse effects, was used in one trial.

3. Results

3.1. The trials

The search process (electronic search, reference list searches, and communication with trialists) identified 60

trials relevant for this review, i.e. treatment trials where a predominantly cholinergic agent had been administered to patients with TD. Thirty-six of these were excluded because they were not randomized controlled trials. These were mainly experimental clinical trials, case series, or case descriptions, mainly conducted during the 1970s and 1980s. Furthermore, four randomized trials used various other medications as comparators but were not placebo-controlled. Overall, the majority of these trials, of which only sporadic ones had been conducted later than 1990, reflected the exploratory state of TD treatment. Results and quality of reporting were variable. All identified trials and detailed reasons for exclusion are reported elsewhere (Tammenmaa et al., 2002).

One randomized controlled trial was excluded because antipsychotic medication was abruptly discontinued for some participants 4 weeks prior to the trial (Simpson et al., 1977). Six trials, which were considered relevant, could not be included since they were of crossover design and incompletely reported. It was impossible to extract first-segment data from these trials, which had investigated lecithin (Domino et al., 1985; Joe et al., 1985; Perez-Cruet et al., 1981), deanol (Jus et al., 1978; Penovich et al., 1978), or CDP-choline (Gelenberg et al., 1989). For one trial investigating 7-methoxyacridine (7-methoxytacrine) (Maršálek et al., 1997), information existed only as statistical end-values (analysis of variance) from which extraction of primary data could not be performed. Every effort was made to retrieve missing data from trialists, and through personal communication, we received additional information about the design and methods of the trials. However, due to the time elapsed, primary data were no longer available.

In addition, one ongoing randomized placebo-controlled trial investigating galantamine was identified (Stanley Caroff, personal communication, March 2002). Results from this trial were unavailable at the time of the review.

Eleven trials (Table 1) met all inclusion criteria and were included in the meta-analysis. Four of the trials investigated lecithin, which contained phosphatidylcholine doses of 20–35 g/day, (Jackson et al., 1979, 1981; Beckham, 1981; Price, 1982; Gelenberg et al., 1990) six trials investigated deanol at doses of 1000–2000 mg/day, (Bockenheimer and Lucius, 1976; Lucius, 1978; Tarsy and Bralower, 1977; Jackson, 1978; de Montigny et al., 1979; Kocher et al., 1980; George et al., 1981) and one trial investigated meclofenoxate at 900 mg/day (Yagi et al., 1990; Ojima et al., 1991). Results from some trials had been published repeatedly and every effort was made to connect papers of the same trials to avoid citation bias.

Considerable variation in length (11 days to 12 weeks) and sample size (5–60 participants) of the trials was present. The total number of randomized participants with a diagnosis of TD in these 11 trials was 261. Of the participants, 59% were male. The concomitant diagnosis was schizophrenia for 77% of participants from the nine trials for which data were available. Other concomitant diagnoses were major affective disorders, anxiety disorders, and organic brain syndromes. The majority of participants were long-term inpatients, recruited from and treated in wards, and most were judged as having moderate to severe TD with a long history of antipsychotic treatment. None of the trials reported use of standardized procedures for diagnosing TD (Schooler and Kane, 1982), but the diagnostic procedures were usually described and well considered. Most participants required concomitant anti-

Table 1
Included randomized placebo-controlled double-blind trials of cholinergic agents in tardive dyskinesia

References	Country	Design	Duration (weeks)	*N*	Age range of patients (years)	Cholinergic drug
Jackson et al., 1979; Jackson et al., 1981	USA	Crossover	2[a]	6	49–60	Lectihin containing phosphatidylcholine 35 g/day
Beckham, 1981	USA	Parallel	11 days	50	23–77	Lecithin containing phosphatidylcholine 33 g/day
Price, 1982	USA	Parallel	11 days	30	26–77	Lecithin containing phosphatidylcholine 33 g/day
Gelenberg et al., 1990	USA	Crossover	8[a]	21	19–70	Lecithin containing phosphatidylcholine 20 g/day
Bockenheimer and Lucius, 1976; Lucius, 1978	Germany	Crossover	5[a]	10[b]	28–75	Deanol 1500 mg/day
Tarsy and Bralower, 1977	USA	Crossover	8[a]	5	mean 54.8	Deanol 2000 mg/day
Jackson, 1978	USA	Crossover	12[a]	6	34–59	Deanol 1500 mg/day
de Montigny et al., 1979	Canada	Parallel	3	20	34–73	Deanol 1500 mg/day
Kocher et al., 1980	Switzerland	Crossover	4[a]	20	42–82	Deanol 1500 mg/day
George et al., 1981	Australia	Parallel	4	33	49–89	Deanol 1000 or 2000 mg/day
Yagi et al., 1990; Ojima et al., 1991	Japan	Parallel	8	60	30–79	Meclofenoxate hydrochloride 900 mg/day

[a] From crossover trials we extracted data from the first segment only.
[b] Originally 20 patients. Antipsychotic medication abruptly changed for 10 subjects due to withdrawal of clozapine in July 1975. Individual data extracted only for the 10 subjects whose antipsychotic medication remained stable during trial.

psychotic medication, but doses were stable. Blinding and consistency of rating procedures were in many trials ensured by rating videotapes of participants, presented to raters in random order.

Eight trials were classified as having a moderate risk of bias since allocation concealment was not described in papers and further information was unavailable. Only three trials (Gelenberg et al., 1990; Bockenheimer and Lucius, 1976; Yagi et al., 1990) were classified as having a low risk of allocation bias based on information available from papers or the trialists.

Of the 11 trials, 6 were of crossover and 5 of parallel design. Incomplete or inextractable reporting of data was encountered in many of these trials. In reports of some parallel trials, variance of outcome measurements was not reported, which is a prerequisite for calculation of precision of pooled continuous data. Every effort was made to use all extractable data.

3.2. Sensitivity analysis of subgroups

Pooled results of trials separated into groups according to compound used (lecithin, deanol, or meclofenoxate), or length of treatment (short-term or long-term) did not show remarkable variation, nor did results of subgroups indicate statistically significant differences between treatment groups. This is partly due to very small sample sizes. Thus, we found it appropriate to pool trials of different lengths and compounds.

3.3. Primary outcomes

Data on any rater-assessed improvement of TD symptoms could be extracted from reports of eight trials. Results from this rather crude binary outcome did not show a statistically significant benefit for cholinergic drugs (N=170, RR=0.84, 95% CI 0.68 to 1.04, p=0.11), albeit this outcome had the largest sample of all primary outcomes (Fig. 1). Another binary outcome of interest was whether improvement was clinically significant, which we predefined as an improvement of 50% in symptom severity. Due to use of nonstandardized scales, results were obtainable from only three trials, and sample size was far too small to give a reliable answer (N=17, RR=0.71, 95% CI 0.43 to 1.16, p=0.17). No obvious benefit or harm of cholinergics was at hand. Seven trials presented results allowing evaluation of whether cholinergics had caused dyskinetic symptoms to increase. Results for this binary analysis showed no statistically significant effect (N=137, RR=1.17, 95% CI 0.55 to 2.50, p=0.7).

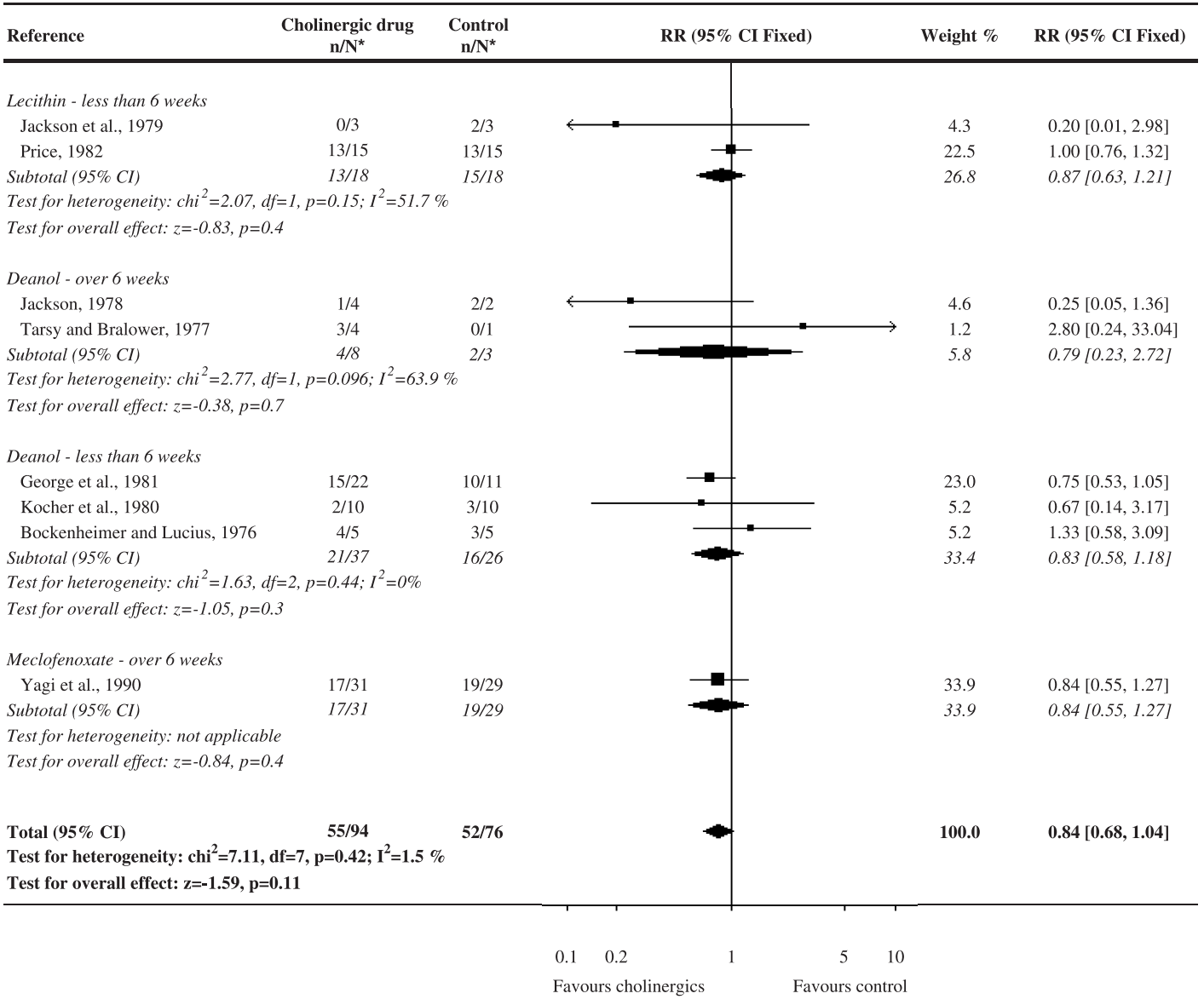
Continuous measures were also used to evaluate the change in TD symptoms at endpoint of trial. Four trials used the AIMS as a means of assessment, and pooled result from these trials, comparing mean endpoint score on AIMS for the group receiving cholinergics with those on placebo, showed no statistically significant effect of cholinergics (N=86, WMD=−0.19, 95% CI −0.53 to 0.14, p=0.3). Sample size was again, however, small. One lecithin trial (Beckham, 1981) assessed endpoint dyskinetic symptoms on the CGI, and no statistically significant differences were observed between groups (N=31, WMD=−0.43, 95% CI −1.36 to 0.50, p=0.4). The SMD was used to pool results measured either by the AIMS or the CGI. Although sample size increased, cholinergics still did not show a significant benefit or harm as compared with placebo (N=117, SMD=−0.24, 95% CI −0.61 to 0.13, p=0.2). One lecithin trial (Price, 1982) used the Rockland TDRS for symptom assessment. Unfortunately, rating data were reported only as statistical end-values (analysis of variance), and therefore, extraction of continuous data could not be performed from this trial. One crossover deanol trial (Tarsy and Bralower, 1977) used a modified Simpson TDRS, however, a statistical comparison was not possible, since the placebo group had only one participant.

3.4. Secondary outcomes

Pooled data on leaving the study early from 10 trials revealed no statistically significant differences between groups (N=240, RR=0.52, 95% CI 0.21 to 1.33, p=0.18). No deaths were reported in 10 trials with a total of 129 patients randomized to receive a cholinergic drug and 111 patients in placebo groups.

We could extract simple binary data on aggravation of psychotic symptoms from five trials, and results from this small sample reveal no statistically significant increase or decrease in risk for aggravated psychosis (N=77, RR=0.50, 95% CI 0.10 to 2.61, p=0.4). However, one trial, for which primary data were unavailable, reported an increase in the Brief Psychiatric Rating Scale schizophrenia score for patients on deanol (de Montigny et al., 1979). This important parameter was evaluated in most trials, but insufficient or absent reporting excludes abundant material from meta-analysis. Other adverse effects were reported heterogeneously and nonsystematically. Deanol was stated to cause nausea or gastric discomfort in some cases, in contrast to the placebo group (de Montigny et al., 1979). Sedation and unspecific motor weakness were observed in the deanol group (de Montigny et al., 1979; George et al., 1981). With regard to adverse effects, no statistically significant difference was found between meclofenoxate and placebo (N=60, RR 0.56, 95% CI 0.15 to 2.14, p=0.4).

Only one trial (Yagi et al., 1990) evaluated global effects of medication on the state of patients using the GUR categorical scale. The binary outcomes extracted from this scale, evaluating usefulness or harmfulness, failed to show a substantial advantage of meclofenoxate (N=60, RR=0.89, 95% CI 0.59 to 1.32), but neither was it demonstrated to be harmful. One trial (Price, 1982) reported binary results on patients' self-reported changes in symptoms. However, these samples were small and showed no statistically significant effect of lecithin (N=30, RR=0.92, 95% CI



RR=risk ratio; CI=confidence interval; Fixed=fixed effect model; Weight %=weight of trial; df=degrees of freedom; p=statistical significance; z=ratio of effect size per standard error.

* For statistical reasons, when calculating risk ratio, n/N indicates the number of patients (n) per total number of patients in treatment group (N) who **did not** have any improvement in their tardive dyskinesia symptoms.

Fig. 1. Any rater-assessed improvement of tardive dyskinesia symptoms in patients treated with cholinergic drugs as compared to placebo.

0.62 to 1.36, p=0.7) or any significant worsening of symptoms (N=30, RR=3.00, 95% CI 0.13 to 68.26, p=0.5) in the comparison between lecithin and placebo.

3.5. Funnel graphs

To accurately demonstrate publication bias, funnel graphs should have data points from a sufficient number of trials. A meaningful funnel plot was available from the outcome "Any improvement in tardive dyskinesia symptoms as assessed by rater", and it did not imply the presence of a publication bias.

4. Discussion

Despite the reasonable number of trials examining the safety and efficacy of cholinergic agents in the treatment of TD, the cumulative data on this clinical question remain inconclusive. Results of meta-analysis provided no evidence of an ameliorating effect of lecithin, deanol, or meclofenoxate on TD symptoms. Nevertheless, a small effect of cholinergic agents cannot be ruled out.

4.1. Recommendations for data reporting

The sample which we were able to include in the statistical analysis was small. Only 11 trials reported data which could be pooled, and the total number of patients evaluated was 261. Unfortunately, reporting of trials was often incomplete, and therefore, we were unable to extract data from all trials. Adherence to the CONSORT recommendation for reporting of clinical trials (Moher et al., 2001) would have increased the dataset available. Groupwise endpoint means and variance measures for each continuous outcome, as well as the number of randomized patients in treatment and control groups, should be clearly reported. If trialists make individual patient data available, or present data from binary parameters in a useful format (Moher et al., 2001), calculating numbers for binary outcomes, such as clinically significant response, becomes possible. Combined results for both segments of a trial are often reported for crossover trials. To avoid the inclusion of a possible carry over effect in meta-analysis (Sibbald and Roberts, 1998), results from each segment should be reported separately.

4.2. Inconclusive heterogeneity and sensitivity analyses

Heterogeneity in the results of trials may reflect differences in study design or sample population rather than true variation in the outcomes of interventions being compared. Results from heterogeneous trials should thus not be pooled, as this may lead to erroneous conclusions of causal relationships. Due to the small sample size in this meta-analysis, meaningful estimations of heterogeneity could not be performed. The same problem was encountered for the predefined sensitivity analyses. It was not possible to evaluate whether the effects of the different compounds varied or what differences a longer treatment course had compared with a short one.

4.3. Special groups at risk of tardive dyskinesia

Old age and liability to develop extra-pyramidal symptoms are risk factors for developing antipsychotic-induced tardive dyskinesia (Glazer, 2000; Jeste, 2000). To elucidate whether the treatment response of these groups at high risk differs from the response in general, subgroup analyses of age-specific groups and of participants with pre-existing other extrapyramidal symptoms would have been pertinent. However, due to shortcomings in published reports and lack of individual patient data, we were not able to explore any specific effects of cholinergic agents in subgroups.

4.4. Efficacy of novel cholinergic agents unresolved

Contemplating the significance of the results of this meta-analysis, it should also be kept in mind that small samples in trials and meta-analyses run the risk of producing beta-errors when treatment effects are small. Furthermore, the actual cholinomimetic properties of lecithin, deanol, and meclofenoxate are controversial and uncertain. Novel cholinergic agents, i.e. donepezil, galantamine, rivastigmine, and tacrine, have been developed for the treatment of dementia. We found only two randomized double-blind controlled trials investigating the effect of novel cholinergic dementia agents, one ongoing galantamine trial (Stanley Caroff, personal communication, March 2002) and a 7-methoxytacrine trial for which primary data were unavailable (Maršálek et al., 1997). Thus, the efficacy of these novel agents in treatment of dyskinetic symptoms has not been investigated extensively.

5. Conclusions

In conclusion, there is no evidence to support the administration of lecithin, deanol, or meclofenoxate to patients suffering from TD. However, if neurobiological research uncovers additional evidence for involvement of central cholinergic deficiency in the pathogenesis of TD, investigation of the clinical effects of novel cholinergic agents on TD symptoms would be warranted. In this case, the effect of these agents should be demonstrated in well-designed, adequately powered, randomized controlled clinical trials.

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