The effects of anticholinergic medications on cognition in children: a systematic review and meta-analysis

Erica Ghezzi1,4, Michelle Chan1,4, Lisa M. Kalisch Ellett2, Tyler J. Ross3, Kathryn Richardson3, Jun Ni Ho2, Dayna Coley1, Claire Steele1 & Hannah A. D. Keage1,4

Cognitive side effects of anticholinergic medications in older adults are well documented. Whether these poor cognitive outcomes are observed in children has not been systematically investigated. We aimed to conduct a systematic review and meta-analysis on the associations between anticholinergic medication use and cognitive performance in children. Systematic review was conducted using Medline, PsychInfo, and Embase, identifying studies testing cognitive performance relative to the presence versus absence of anticholinergic medication(s) in children. We assessed effects overall, as well as relative to drug class, potency (low and high), cognitive domain, and duration of administration. The systematic search identified 46 articles suitable for meta-analysis. For the most part, random effects meta-analyses did not identify statistically significant associations between anticholinergic exposure and cognitive performance in children; the one exception was a small effect of anticholinergic anti-depressants being associated with better cognitive function (Hedges’ g = 0.24, 95% CI 0.06–0.42, p = 0.01). Anticholinergic medications do not appear to be associated with poor cognitive outcomes in children, as they do in older adults. The discrepancy in findings with older adults may be due to shorter durations of exposure in children, differences in study design (predominantly experimental studies in children rather than predominantly epidemiological in older adults), biological ageing (e.g. blood brain barrier integrity), along with less residual confounding due to minimal polypharmacy and comorbidity in children.

Anticholinergic medications are commonly prescribed1–3 yet a growing body of evidence has demonstrated that their use is associated with a higher risk of incident cognitive impairment4–6. This literature has been reviewed multiple times in older adults, whereby anticholinergic medications have been consistently associated with cognitive decline and dementia7–9. There has been no systematic synthesis of the cognitive effects of anticholinergic medications in children.

There are few population-based studies that have assessed the extent to which children are exposed to anticholinergic medicines1. Most studies examining anticholinergic medicines in children have focussed on the use of medicine classes for specific indications, for example, asthma or overactive bladder, rather than providing population-based estimates for the use of anticholinergic medicines like the studies in older adults. Approximately 11% of Australian children have a current diagnosis of asthma10 and up to 20% of children experience bedwetting11 so there is potential for a high prevalence of use of anticholinergic medicines to treat these conditions in children. One population based study from Slovenia reported that 20% of children using prescription medicines were dispensed anticholinergic medicines, most commonly antihistamines1.

Anticholinergic medications refer to a broad class of medicines which block the neurotransmitter acetylcholine12. These medications are used in the treatment of many conditions such as depression, vertigo, asthma, cardiac arrhythmias and incontinence. High potency anticholinergic medications appear to most detrimentally affect cognition in older adults (as compared to low potency)13. Further, the class of anticholinergic medication differentially associates with cognitive decline in late-life, with anti-depressants (amitriptyline, amiodarone, etc.).
dosulepin, paroxetine), urologicals (oxybutynin, tolterodine), and antiparkinsonian drugs showing the strongest associations with incident dementia. Neurobiologically, the cholinergic system primarily mediates attentional processes and therefore could be expected to be primarily impaired by anticholinergic medications, although cognitive domain specific effects have not been investigated.

The current study aims to quantitatively synthesise the literature on associations between anticholinergic medications and cognitive performance in children. Findings from this review will inform medical practitioners of any risks (or lack thereof) associated with anticholinergic use in children, and subsequently help to inform the safe prescribing of anticholinergics. It is critical to identify whether anticholinergics should be prescribed with restraint in children. We hypothesise that in children (1) exposing to anticholinergic medications will be significantly negatively associated with performance on cognitive tests, and that associations will be strongest for (2) antidepressant and urological drug classes (as compared to other drug classes), (3) high-potency anticholinergics (as compared to low-potency), (4) those exposed long-term (as opposed to short-term) and (5), within the cognitive domain of attention.

Methods

Search strategy. This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplementary Table 1 for PRISMA Checklist). A systematic literature search was conducted in December 2019 using the electronic databases Medline, PsychInfo, and Embase. The search strategy used a combination of keywords for anticholinergic medications (see Supplementary Material), cognition terms (cognit* OR neuropsych* OR learn* OR memory OR “executive function” OR “executive functions”) and demographic terms (children OR childhood OR youth* OR teen*). No published review protocol exists for the current study.

Anticholinergic medications were defined as medicines with clinically significant anticholinergic properties as listed in a systematic review by Duran et al. Medications assessed by the Duran systematic review to be of either high or low anticholinergic potency, but not ambiguous potency, were included. Studies were screened and assessed for eligibility by two independent reviewers, first by title and abstract, then by full text, according to inclusion and exclusion criteria described below (MC, TJR, DC, CS and JNH). Any conflicts were resolved through consensus.

Inclusion and exclusion criteria. Studies of either within- or between-groups design were included if they reported at least one cognitive outcome for both children exposed and unexposed to anticholinergic medications; reported data for a sample of children (< 18 years old); were published in English; and were published in peer-reviewed journal articles. Studies from all publication years were accepted. “On” medication participants included children exposed to at least one anticholinergic medication. “Off” medication participants included matched controls unexposed to any other medication, participants treated with placebo, participants undergoing withdrawal from the medication, or the baseline measurements of the exposed group. To be eligible for inclusion, studies needed to report cognitive outcomes based on objective cognitive measures; subjective behavioural reports were not included (e.g. self, parent or teacher reports of cognitive functioning). Studies were excluded if the control group did not share the same disorder or symptom (i.e. healthy control group) of the experimental group. Studies which only compared the effects of anticholinergic medication versus non-anticholinergic medication, rather than anticholinergic medication versus no medication, were excluded. Studies were also excluded if they involved non-human (animal) participants; if they assessed in-utero anticholinergic exposure; or if they were a case report, case series, thesis or conference abstract.

Data extraction. Data were extracted from eligible studies independently by one reviewer (EG, MC, TJR) and then checked by a second reviewer, with any discrepancies resolved through discussion or checked again (by a third reviewer). Extracted data include country of publication, study design, sample size (and number of male/ female participants), age, diagnost of sample, name of medication, duration of administration, and cognitive domains assessed. The extracted medication name was then classified by potency and drug class by an academic pharmacist (LE). Data required for meta-analysis were also extracted. This included any data for which an effect size (standardised mean difference) could be calculated for differences between on and off medication groups (e.g., means and standard deviations, Cohen’s d and confidence intervals (CIs), sample size and correlation statistic, means and correlation statistic, or means and p-value).

Quality assessment. A quality assessment tool was developed for this study, adapted from a critical appraisal tool for randomised controlled trials from the Joanna Briggs Institute, see Supplementary Material—Quality Assessment Tool. The Joanna Briggs Institute is a highly regarded organization with recommended well-used critical appraisal checklists. The quality assessment tool comprised an eight-point checklist. All studies were screened using this tool by two independent reviewers (MC and TJR) and any conflicts in scoring were resolved through discussion.

Statistical approach. Some included studies reported data for both within- and between-groups designs. For example, they may include two groups: one that experiences a period of on and off medication, and one non-medicated control group. In these cases, the between-group design (i.e. medication versus control) was preferentially selected in order to minimise the effect of cognitive development (over time). Where one study reported both within- and between-group comparisons for two distinct participant samples (i.e. one group both on and off medication, along with a second group on medication and a third no-medication control group) both within- and between-groups data were extracted. In cases where one study reported both (within and between)
comparisons over multiple time-points, within-groups data were extracted for any time-points where between-groups data were unavailable.

All outcome measures were standardised using Hedges’ $g$ for difference between on- and off-medication groups. A positive Hedges’ $g$ represents a better cognitive score for the on-medication group compared to the off-medication group, regardless of the direction of the original cognitive test. Small, medium, and large effect sizes were classified using the Hedges and Olkin method, as 0.20, 0.50, and 0.80 respectively. Comprehensive Meta-Analysis software (version 3) was used to calculate effect sizes, structures of Hedges’ $g$ are dependent on study design (within- or between-groups). Statistical analyses were conducted using the meta package for R (Version 4.0.2). Dependency was present in analyses due to included studies reporting multiple cognitive outcomes or time-points for follow-up based on the same, or largely overlapping, participant samples. This was accounted for by averaging across effect sizes within studies, so one effect size was used per study within each analysis. The data and script associated with this analysis are publicly available (https://github.com/ericaghezzia/anticholinergic_med_metaanalysis).

Outcomes across studies were pooled using a random-effects model. The commonly used DerSimonian and Laird estimator of between-study variance has been criticised due to its propensity to underestimate the true between-study variance, leading to narrow CIs and potential false-positive estimations. Hence, we followed the recommendation of Veroniki et al. and employed the Paule and Mandel method, which has been shown to be less biased when estimating between-study variance. Sensitivity analyses revealed no substantial differences in outcomes when analyses were run using common between-groups estimators. The Hartung-Knapp method for random effects meta-analysis was also applied to all analyses. A result was considered statistically significant when $p < 0.05$. We considered this an exploratory study and did not correct for multiple comparisons. Between-study variance was quantified using $\tau^2$. The proportion of between-study heterogeneity out of total variance was assessed using the $I^2$ statistic. Values of $I^2$ were classified as low (25%), moderate (50%), or high (75%).

Subgroup analysis. Subgroup analyses were stratified by anticholinergic potency, cognitive domain, drug class, and duration of medication administration. Anticholinergic potency was classified as low or high according to Durán et al. Cognitive domain was based on Lezak et al., attention, psychomotor functioning, concept formation and reasoning, perception, memory, executive function, language, and intelligence. The anticholinergic drugs administered were categorised by class as antiepileptics (WHO Anatomical Therapeutic Chemical code N03), antiparkinsonian medicines (N04B), antipsychotics (N05A), antidepressants (N06A), respiratory medicines (R), opioid analgesics (N02A), or urological medicines (G04B). Only one study reported results based on an antiparkinsonian anticholinergic, so subgroup analysis for this medication class was not conducted (note: the study was included in the overall meta-analysis). Total volume of exposure or dose has been shown to be important in assessing risk of cognitive impairment associated with use of anticholinergic medicines in adults; however, dose was inconsistently reported, or not reported at all, in many of the studies included in the meta-analysis. Duration of exposure, which was consistently reported in the studies, was therefore analysed. Duration of medication administration was categorised as either (1) current and long-term (>1-month), (2) current and acute (≤1-month), and (3) historical administration. Each subgroup analysis was based on a random-effects model, where calculations of within-subgroup variance and comparisons between subgroups were both made using a random-effects model. Fixed effects comparisons of differences between subgroups were not made due to the risk of false positives. The $Q$ statistic was calculated as a test of between-subgroups differences.

Publication bias. Funnel plots of effect size versus standard error for the primary outcome were visually examined for symmetry to assess for bias across studies due to the small-study effect. As the whole meta-analysis contained at least 10 studies, small-study effect was formally tested using Egger’s test of the intercept. If evidence of asymmetry was found (one-tailed $p < 0.1$ on the Egger’s test), Duval and Tweedie’s trim and fill method would have been used to quantify the magnitude of potential bias.

Results

Summary of studies. A total of 7,645 articles were identified, of which 6,283 were screened by title and abstract following duplicate removal. Full-text review was conducted on 323 articles, and 46 of these were included for final review and meta-analysis (Fig. 1). The 46 included studies were published across 6 decades, with 1, 2, 7, 10, 13, and 13 studies published in ascending decades from the 1960s. Of the included studies, 37 were conducted in developed countries, 7 in developing countries, and 2 included children from both developing and developed countries (classified according to the UN). For a complete overview of the characteristics of included studies, see Table 1.

Overall cognition. Overall, the 46 studies included reported a total of 536 effect sizes. The pooled effect size of the difference between cognition on and off medication across the 46 studies was negligible and non-significant ($g = 0.05$, 95% CI $-0.02$ to 0.11, $p = 0.16$; see Fig. 2), with no heterogeneity between studies ($\tau^2 = 0$, $I^2 = 0$%, $Q = 42.36$). The funnel plot did not reveal significant asymmetry (Egger’s intercept = $-0.5$, $p = 0.14$; see Fig. 3).

Subgroup analyses. Pooled estimates for subgroup analyses by anticholinergic drug class, potency, length of administration and cognitive domain are presented in Table 2. The number of studies within individual sub-analyses ranged from 2 to 37. Varying levels of heterogeneity were present across analyses, ranging from null to high ($\tau^2$ range: 0.07–0.13, $I^2$ range: 0–76.2, $Q = 0.18$–54.70).

No significant differences between subgroups were revealed through a test of between-subgroup differences using the random-effects model (see Table 2). The pooled effect size for cognitive outcomes on antidepressant medications was small and statistically significant (see Table 2 and Fig. 4), with negligible heterogeneity between
studies ($\tau^2 = 0$, $I^2 = 13.2\%$, $Q = 6.91$). Notably, this effect was not significant in a sensitivity analysis (Supplementary Table 3) which included only studies of high quality. Pooled estimates were non-significant across the remaining anticholinergic drug class (see Fig. 4), potency (see Fig. 5), length of administration (see Fig. 6), and cognitive domain (see Fig. 7) subgroup analyses. All null results were replicated within the sensitivity analysis of high-quality studies, except the memory cognitive domain analysis, which had a small positive significant effect ($g = 0.09$, 95% CI 0.01–0.17, $p = 0.02$).

**Discussion**

We quantified the effects of anticholinergic medications on cognition in children systematically across the literature. We report that, unlike older adult samples, anticholinergic medications are not associated with cognitive impairments in children. This finding was regardless of the classification approach used: drug class, potency, duration of use, and cognitive domain. The discrepancy between child and older adult samples may be due to shorter lengths of exposure in children, higher rates of polypharmacy in older adults, residual confounding, study design, or biological ageing processes.

Older adults have the opportunity for years or decades of anticholinergic exposure, with polypharmacy common, whereas studies included here from child samples typically had short exposure durations (6 months or less in most studies) and little polypharmacy. It may be that the detrimental effect of anticholinergic medications on cognition in late-adulthood is driven by long exposure and polypharmacy, factors not observed in children. Further, in late-life, the class of antidepressant appears to differentially affect cognition, with anti-depressants, urologicals, and antiparkinsonian drugs showing the strongest associations with incident dementia risk. We did not see this pattern of effects in children. It may be that duration of exposure and polypharmacy again drives this difference, however residual confounding in late-life samples cannot be ruled out. It may be that incontinence and mood symptoms, for which anticholinergic medications are prescribed, are early clinical indicators of dementia-related neuropathologies (which accrue decades prior to a dementia diagnosis) and that early, undiagnosed dementia is driving the associations between use of anticholinergic medicines and poor cognition in adults.

Interestingly, all study designs included in this review were experimental, whereas those included in reviews of older adults are typically longitudinal epidemiological cohort studies. Standards of reporting cognitive

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**Figure 1.** PRISMA flow diagram of the article selection and screening process. The databases searched were Medline, PsychInfo, and Embase.
| Author et al. | Year | Country | Design | Sample N (M/F) | Age in years* | Diagnoses | Name | Potency | Class/ function | Length of administration | Medication duration | Cognitve domain(s) |
|-------------|------|---------|--------|--------------|--------------|-----------|------|--------|-----------------|------------------------|-----------------|------------------|
| Aldenkamp et al. | 1993 | Sweden | NRCT (Within) | 83 (47/36) | 12.8 (2.4) | Epilepsy | Carbamazepine | Low | Antiepileptic | Long | > 1 year | Att., PM |
| Aman et al. | 2008 | USA | RCT (Between)** | 38 (29/9) | 9.4 (3.0) | Autism + Severe behavioural disturbance | Risperidone | Low | Antipsychotic | Acute, Long | 4 weeks, 8 weeks | Att., CF + R, Mem., Perc., PM |
| Aman et al. | 2009 | USA | RCT (Cross-over) | 16 (14/2) | 8.6 (2.6) | DRD/ADHD/High-functioning autism | Risperidone | Low | Antipsychotic | Acute | 2 weeks | Att., PM |
| Barrickman et al. | 1991 | USA | NRCT (Within) | 19 (16/3) | 11.0 (2.3) | ADHD | Fluoxetine | Low | Antidepressant | Long | 6 weeks | Att., EE, Int |
| Beers et al. | 2005 | USA | RCT (Between)** | 13 | 11.9 (3.0) | TBI | Amanantadine | Low | Antiparkinsonian | Long | 12 weeks | Att., CF + R, EF |
| Bender and Milgrom | 2004 | USA | RCT (Between) | 60 [8–17] | | SAR | Loratadine | Low | Respiratory | Acute | 2 weeks | Att., Mem |
| Bender et al. | 1991 | USA | NRCT (Between) | 63 | 11.7 (2.1) | Asthma | Theophylline | Low | Respiratory | Acute | 1 week, 1 month, 3 months, 6 months | Att |
| Carlson et al. | 1992 | USA | NRCT (Crossover) | 11 (8/3) | 8.7 (2.4) | CD with manic symptoms/CD with family RPD history/Agressive behaviour | Lithium | Low | Antipsychotic | Acute, Long | 4 weeks, 8 weeks | Att., EF + R, Mem |
| Chen et al. | 2001 | Taiwan | NRCT (Within) | 25 (13/12) | 11.2 (2.0) | Epilepsy | Carbamazepine | Low | Antiepileptic | Long | > 1 year | Int |
| de Graaf et al. | 2011 | Netherlands | RCT (Between) | 90 (51/39) | < 3d at exposure, 5 at follow up | Pain | Morphine | Low | Opioid analgesic | History | NR | Att., Mem, Perc., PM |
| de Graaf et al. | 2013 | Netherlands | RCT (Between) | 89 (56/33) | < 3d at exposure, 8 – 9 at follow-up | Pain | Morphine | Low | Opioid analgesic | History | NR | Att., CF + R, EE, Int., PM |
| Donati et al. | 2007 | Europe (7 countries) | RCT (Within) | 83 (37/46) | 10 [6–16] | Partial seizures | Oxcarbazepine, Carbamazepine | Low | Antiepileptic | Long | 6 months | Att., Mem, Perc., PM |
| Erickson et al. | 1984 | USA | RCT (Within) | 11 | 14.2 (12.9–18.6) | Schizophrenia/ Schizophreniform disorder | Thioridazine, Thiothixene | High | Antipsychotic | Long | 35 days | Att |
| Eun et al. | 2012a | South Korea | RCT (Within) | 41 (24/17) | 8.3 (2.1) | Epilepsy | Carbamazepine | Low | Antiepileptic | Long | 32 weeks | Int |
| Eun et al. | 2012b | South Korea | NRCT (Within) | 168 (98/70) | 8.4 (2.7) | Epilepsy | Oxcarbazepine | Low | Antiepileptic | Long | 26–32 weeks | Att., Int., CF + R, Lan., PM |
| Farmer et al. | 2017 | USA | RCT (Between) | 165 (128/35) | 8.9 (2.0) | ADHD + Severe physical aggression | Risperidone | Low | Antipsychotic | Acute | 3 weeks | Att |
| Ferguson et al. | 2012 | USA | RCT (Between) | 19 (12/7) | Neonate exposure; 6.2 (0.3) at follow-up | Pain | Morphine | Low | Opioid analgesic | History | ≤ 14 days | Att., CF + R, Int., Lan |
| Forsythe et al. | 1991 | UK | RCT (Between) | 14 (7/7) | 10 | Epilepsy | Carbamazepine | Low | Antiepileptic | Acute, Long | 1 month, 6 months, 12 months | Att., Mem |
| Freeberg et al. | 1968 | Canada | RCT (Between)** | 36 (36/0) | 8.7 (6–12) | Hyperactivity | Chlorpromazine | High | Antipsychotic | Long | 74.8 days | CF + R |
| Giramonti et al. | 2008 | USA | RCT (Crossover) | 14 (9/5) | 7.7 (2.0) | Incontinence | Oxybutynin, Tidodermine | High | Urological | Acute | 2 weeks | Att., Mem |
| Gualtieri and Evans | 1988 | USA | RCT (Crossover) | 9 (6/3) | 9.5 (1.3) | ADHD | Imipramine | High | Antidepressant | Acute | 2–3 days | Att, PM |
| Gualtieri et al. | 1991 | USA | RCT (Crossover) | 12 (11/1) | 6–12 | ADHD | Desipramine | High | Antidepressant | Acute | 2–3 days | Att., Mem, PM |
| Gunther et al | 2006 | Germany | NRCT (Within) | 23 (21/2) | 11.9 (2.1) | ADHD + DBD | Risperidone | Low | Antipsychotic | Acute | 4 weeks | Att., EF |
| Jung et al. | 2015 | South Korea | RCT (Within) | 40 | 15 [5–26] | Epilepsy | Carbamazepine | Low | Antiepileptic | Long | 52 weeks | Int |
| Klein | 1990 | USA | RCT (Within & Between) | 36 (33/3) | 8.5 (1.6) | ADHD + Hyperactivity | Thioridazine | High | Antipsychotic | Acute, Long | 4 weeks, 12 weeks | Att., CF + R, EF, Int., Lan., Mem., Perc., PM |
| Kwon et al. | 2013 | South Korea | NRCT (Between)** | 29 (17/15) | 8.4 (2.3) | Epilepsy | Oxcarbazepine | Low | Antiepileptic | Long | 6 months | Att., CF + R, EE, Int |
| O'Dougherty et al. | 1987 | USA | NRCT (Within) | 11 (4/7) | 9.8 (3.1) | Epilepsy | Carbamazepine | Low | Antiepileptic | Long | 3 weeks–10 months | Att., Mem, PM |
| Opper te et al. | 2020 | Italy | NRCT (Within) | 46 (16/20) | 9.8 (2.3) | Epilepsy | Oxcarbazepine, Carbamazepine | Low | Antiepileptic | Long | 9 months | Comp |

Continued
Table 1. Demographic, sample, anticholinergic medication and cognitive outcome characteristics for included studies within meta-analysis for cognitive outcomes on and off anticholinergic medication. *Age reported as mean (SD or range) or median [range]. **Sufficient data available for both within- and between-groups design. Selection was made using protocol outlined in "Methods". Studies without description of gender split did not report this information in their original study.

| Author          | Year | Country          | Design          | Sample | Anticholinergic medication | Mediation duration | Cognitive domain(s) |
|-----------------|------|------------------|-----------------|--------|-----------------------------|--------------------|---------------------|
| Pandina et al.  | 2009 | Europe (6 countries), Israel, South Africa | RCT (Within & Between) | 284 (248/36) | 10.8 (2.9) | DBD | Risperidone | Low | Antipsychotic | Long | 6 weeks, 6 months | Att., Mem |
| Piccinelli et al. | 2010 | Italy | NRCT (Within) | 43 (21/22) | 10.4 (3.1) | Epilepsy | Carbamazepine | Low | Antiepileptic | Long | 12 months | CF + R, Int |
| Platt et al.    | 1981 | USA | RCT (Between**) | 30 (28/2) | 9.0 (5.8–12.9) | CD | Haloperidol, Lithium | Low | Antipsychotic | Acute | 4 weeks | Att., EF |
| Platt et al.    | 1984 | USA | RCT (Between**) | 61 (57/4) | 9.0 (5.2–12.9) | CD | Haloperidol, Lithium | Low | Antipsychotic | Acute | 4 weeks | Att., EF |
| Rappaport et al. | 1989 | USA | RCT (Crossover) | 17 (11/6) | [6–12] | Asthma | Theophylline | Low | Respiratory | Acute | 3.5 days | Att., EF, Mem, PM |
| Robles et al.   | 2011 | Spain | RCT (Within) | 49 (38/11) | 15.9 (1.4) | Psychosis | Quetiapine, Clonazapine | Low | Antipsychotic | Long | 6 months | Att., CF + R, Comp, EE, Mem., Perc., PM |
| Schlieper et al. | 1991 | Canada | RCT (Crossover) | 31 (21/10) | 9.8 (1.6) | Asthma | Theophylline | Low | Respiratory | Acute | 10 days | Att., EF Mem |
| Seidel and Mitchell et al. | 1999 | USA | NRCT (Crossover) | 10 (6/4) | 9.7 (2.0) | Epilepsy | Carbamazepine | Low | Antiepileptic | Long | 2.2 months–2.1 years | Att., CF + R, Int., Lan., Mem., PM |
| Shehab et al.   | 2016 | Lebanon | NRCT (Within) | 24 (8/16) | 14.8 (1.6) | MDD | Fluoxetine | Low | Antidepressant | Long | 6 weeks, 12 weeks | Att., EF |
| Sommer et al.   | 2005 | USA | NRCT (Between**) | 25 (11/14) | 7.2 (1.8) | Incontinence | Oxybutynin | High | Urological | Acute | 4 weeks | Att., Mem |
| Stevenson et al. | 2002 | Europe (12 countries), Brazil, Argentina, Canada | RCT (Between) | 165 | 2.92 | Dermatitis | Cetrizine | Low | Respiratory | Long | 8 weeks | Comp |
| Tornby et al.   | 1994 | Sweden | NRCT (Within) | 100 (56/44) | 12.5 (2.1) | Epilepsy | Carbamazepine | Low | Antiepileptic | Long | Approx. 3.7 years | Att., Mem., PM |
| Troost et al.   | 2006 | Netherlands | RCT (Within) | 24 (22/2) | 9.3 (2.6) | FDD | Risperidone | Low | Antipsychotic | Acute, Long | 4 weeks, 8 weeks, 24 weeks | Att |
| Tsirridou et al. | 2005 | Greece | NRCT (Within) | 70 (45/25) | 8.4 (1.2) | Epilepsy | Ocarbazepine | Low | Antiepileptic | Long | 18 months | Att., CF + R, Lan., PM |
| Werry et al.    | 1975 | New Zealand | RCT (Crossover) | 21 (21/0) | 8.7 (1.7) | Incontinence | Imipramine | High | Antidepressant | Acute | 3 weeks | Att |
| Wilson and Station et al. | 1984 | USA | NRCT (Within) | 75 (55/20) | 10.8 (5.5–16.0) | MDD | Amitriptyline, Imipramine | High | Antidepressant | Long | >3 months | Att., CF + R, EE Int., Lan., PM |
| Yees et al.     | 1977 | USA | RCT (Crossover) | 22 (21/1) | 9.2 (7.3–12.3) | Hyperactivity/ aggressive behaviour | Amitriptyline, Imipramine | High | Antidepressant | Acute | 2 weeks | Att., EF |
| Yuan et al.     | 2018 | China | RCT (Between**) | 124 (85/39) | 6.5 (2.0) | ID | Lithium | Low | Antipsychotic | Long | 3 months | Int |

performance also differ between children and adults. Cognitive performance in children is typically reported as test scores on a continuum, while in adults (especially those in late-life), a dichotomous classification of Neurocognitive Disorders is primarily used (e.g. presence versus absence of mild cognitive impairment or dementia). Study designs and differences in classification of cognition therefore may also underlie differences in the patterns of effects observed in children versus older adults, including the finding that anticholinergic antidepressants displayed a positive association with cognition (albeit with a small effect size, which was not significant when only high-quality studies were included). This small positive effect may be due to the short-term nature of the studies included here and is consistent with a meta-analysis of randomised control trials in adult samples. We do not
**Figure 2.** Forest plot for overall cognition analysis.

**Figure 3.** Funnel plot for overall cognition analysis.
know the effects of the long-term use anticholinergic antidepressants in children. Notably, a small positive effect of anticholinergic medication on memory was found when only including studies of high quality. Whether this is a true effect, which is counter to that found in adults\textsuperscript{93,94}, needs to be replicated in future studies. Lastly, there are important biological differences between children and adults that would modify the psychopharmacological effects of anticholinergic medications, particularly blood brain permeability\textsuperscript{94,95}.

This study is not without limitations. The included studies were biased in terms of geographical representativeness. Fourteen studies were excluded at the full-text stage as they were not in English (of 323) and we do not know if any would have met inclusion criteria; although, given the low number, they would unlikely have changed the conclusions. Authors of papers were contacted, but we either had no response or the author was unable to provide us with the necessary data where it was not presented in text. We assessed the effect of duration of exposure on cognitive outcomes, when total dose or volume of exposure may have been more appropriate. However, this information was inconsistently reported or not reported at all in many of the studies. Therefore, duration of use was used as the best proxy for volume of exposure, with the assumption that longer duration of use would equate to higher volume of exposure. Only 21 of the 100 high- or low-potency anticholinergics identified in a systematic review of anticholinergic medications by Duran et al.\textsuperscript{12} were used in the studies included in this meta-analysis. It may be that different results would be seen had children been exposed to a wider range of anticholinergic medicines. Positively, the vast majority of studies (all but two) utilised valid and reliable cognitive outcome measures, as catalogued specifically or adapted from those detailed in Lezak et al.\textsuperscript{96}.

Table 2. Pooled estimates for subgroup analyses by anticholinergic drug class, potency, length of administration and cognitive domains.

| Subgroup analysis          | Pooled estimate | Heterogeneity | Test of between-subgroups differences |
|---------------------------|-----------------|---------------|---------------------------------------|
| Drug class                |                 |               |                                       |
| Antiepileptic             | 14, −0.03       | 0.63          | 0.08                                  |
| Antipsychotic             | 14, 0.06        | 0.19          | 0.44                                  |
| Antidepressant            | 7, 0.24         | 0.04          | 0.19                                  |
| Respiratory               | 5, 0.02         | 0.75          | 0.14                                  |
| Opioid analgesic          | 3, −0.18        | 0.34          | 0.18                                  |
| Urological                | 2, −0.13        | 0.52          | 0.18                                  |
| Potency                   |                 |               |                                       |
| Low                       | 36, 0.02        | 0.50          | 0.40                                  |
| High                      | 10, 0.11        | 0.29          | 0.12                                  |
| Length of administration  |                 |               |                                       |
| Current and long-term     | 29, 0.07        | 0.19          | 0.40                                  |
| Current and acute         | 20, 0.05        | 0.25          | 0.86                                  |
| Historical                | 3, −0.18        | 0.34          | 0.18                                  |
| Cognitive domain          |                 |               |                                       |
| Attention                 | 37, 0.04        | 0.32          | 0.40                                  |
| Psychomotor functioning   | 17, −0.10       | 0.32          | 0.43                                  |
| Concept formation and reasoning | 13, 0.14       | 0.08          | 0.40                                  |
| Perception                | 3, 0.25         | 0.45          | 0.11                                  |
| Memory                    | 16, 0.04        | 0.40          | 0.12                                  |
| Executive function        | 15, −0.01       | 0.91          | 0.27                                  |
| Intelligence              | 14, 0.08        | 0.53          | 0.54                                  |
| Language                  | 6, 0.11         | 0.17          | 0.54                                  |

Conclusion

By pooling effects across previous literature, anticholinergic medications do not appear to detrimentally affect cognitive function in children. In fact, there may be a small positive cognitive benefit of anticholinergic antidepressants, at least in the short-term. Our findings appear to conflict with reviews in older adults, and future studies will have to disentangle the reasons for this.
| Study          | Hedges' g  | 95% CI    |
|----------------|------------|-----------|
| Antiepileptic  |            |           |
| Kwon 2013      | -0.70      | [-1.46; 0.07] |
| O'Dougherty 1987 | -0.52      | [-1.51; 0.47] |
| Roccelli 2010  | -0.50      | [-1.44; 0.44] |
| Aldenkamp 1993 | -0.30      | [-1.04; 0.42] |
| Tonnby 1994    | -0.33      | [-0.70; 0.04] |
| Otero 2019     | -0.18      | [-0.59; 0.27] |
| Donati 2007    | -0.05      | [-0.52; 0.42] |
| Chen 2001      | -0.01      | [-0.56; 0.53] |
| Seidel 1999    | 0.03       | [-0.56; 0.63] |
| Eun 2012b      | 0.04       | [-0.30; 0.37] |
| Jung 2015      | 0.04       | [-0.40; 0.47] |
| Forsthe 1991   | 0.05       | [-0.63; 0.72] |
| Tzitzidou 2005 | 0.12       | [-0.17; 0.42] |
| Eun 2012a      | 0.29       | [-0.02; 0.60] |
| Overall effect | -0.03      | [-0.17; 0.11] |
| Antipsychotic  |            |           |
| Erickson 1984  | -0.48      | [-1.27; 0.30] |
| Klein 1990     | -0.06      | [-0.53; 0.41] |
| Farmer 2017    | -0.02      | [-0.34; 0.30] |
| Pandine 2009   | 0.02       | [-0.15; 0.20] |
| Yuan 2019      | 0.03       | [-0.32; 0.38] |
| Carlsson 1992  | 0.11       | [-0.89; 1.11] |
| Amman 2009     | 0.13       | [-0.36; 0.63] |
| Platt 1981     | 0.13       | [-0.74; 1.01] |
| Robles 2011    | 0.15       | [-0.50; 0.81] |
| Freiberg 1968  | 0.18       | [-0.71; 1.08] |
| Platt 1984     | 0.20       | [-0.43; 0.82] |
| Gunther 2006   | 0.31       | [-0.26; 0.86] |
| Amman 2008     | 0.41       | [-0.35; 1.18] |
| Troost 2006    | 0.89       | [-0.04; 1.41] |
| Overall effect | 0.06       | [-0.03; 0.16] |
| Antidepressant |            |           |
| Guaita 1988    | -0.29      | [-1.36; 0.78] |
| Guaita 1991    | -0.09      | [-0.59; 0.71] |
| Werry 1975     | -0.08      | [-0.50; 0.33] |
| Yepes 1977     | 0.18       | [-0.44; 0.79] |
| Barrickman 1991 | 0.22     | [-0.23; 0.68] |
| Shehah 2016    | 0.29       | [-0.37; 0.88] |
| Wilson 1984    | 0.45       | [-0.21; 0.89] |
| Overall effect | 0.24       | [0.01; 0.47] |
| Respiratory    |            |           |
| Schieper 1991  | -0.07      | [-0.58; 0.43] |
| Bender 2004    | -0.05      | [-0.66; 0.56] |
| Stevenson 2002 | -0.02      | [-0.33; 0.28] |
| Rappaport 1989 | 0.01       | [-0.45; 0.47] |
| Bender 1991    | 0.33       | [-0.21; 0.86] |
| Overall effect | 0.02       | [-0.15; 0.19] |
| Opioid analgesic|          |           |
| de Graaf 2011  | -0.38      | [-0.80; 0.04] |
| Ferguson 2012  | -0.10      | [-1.10; 0.89] |
| de Graaf 2013  | 0.04       | [-0.41; 0.50] |
| Overall effect | -0.16      | [-0.79; 0.48] |
| Urological     |            |           |
| Sommer 2005    | -0.23      | [-1.01; 0.55] |
| Giramonti 2008 | 0.06       | [-0.96; 1.05] |
| Overall effect | -0.13      | [-1.83; 1.58] |

Figure 4. Forest plot for medication class sub-analysis.
Figure 5. Forest plot for anticholinergic potency sub-analysis.
Figure 6. Forest plot for length of administration sub-analysis.
### Figure 7. Forest plot for cognitive domain sub-analysis.

| Study | Hedges' g | 95% CI |
|-------|-----------|--------|
| Attention | | |
| Erikson 1964 | -0.49 | [-1.27; 0.30] |
| Tonby 1994 | -0.39 | [-0.77; 0.02] |
| Kwon 2013 | -0.38 | [-1.13; 0.38] |
| Aldenkamp 1993 | -0.38 | [-1.02; 0.27] |
| Ferguson 2012 | -0.26 | [-1.26; 0.74] |
| O'Dougherty 1987 | -0.23 | [-1.18; 0.72] |
| Guatelli 1991 | -0.22 | [-1.01; 0.58] |
| Seidel 1999 | -0.15 | [-0.74; 0.44] |
| Bender 2004 | -0.13 | [-0.74; 0.48] |
| Schlieper 1991 | -0.11 | [-0.60; 0.38] |
| de Graaf 2013 | -0.09 | [-0.55; 0.36] |
| Werry 1975 | -0.08 | [-0.50; 0.33] |
| Sommer 2005 | -0.08 | [-0.56; 0.70] |
| Klein 1990 | -0.08 | [-0.55; 0.40] |
| Donati 2007 | -0.50 | [-0.49; 0.90] |
| Tzirindou 2005 | -0.05 | [-0.38; 0.28] |
| Beers 2005 | -0.04 | [-1.16; 1.07] |
| Farmer 2017 | -0.02 | [-0.34; 0.30] |
| Pandina 2009 | -0.01 | [-0.19; 0.17] |
| Guatelli 1991 | -0.00 | [-1.15; 1.15] |
| Barrickman 1991 | -0.00 | [-0.45; 0.45] |
| Forsythe 1991 | 0.00 | [-0.68; 0.68] |
| Aman 2009 | 0.04 | [0.45; 0.52] |
| Rapaport 1989 | 0.04 | [-0.42; 0.49] |
| Robles 2011 | 0.05 | [0.53; 0.73] |
| Eun 2012b | 0.11 | [-0.22; 0.44] |
| Giramonti 2008 | 0.12 | [-0.88; 1.11] |
| Yepes 1977 | 0.20 | [-0.41; 0.80] |
| Carlson 1992 | 0.21 | [-0.78; 1.19] |
| Shehab 2016 | 0.22 | [-0.40; 0.84] |
| Aman 2008 | 0.24 | [-0.51; 0.96] |
| Platt 1981 | 0.15 | [-0.40; 1.11] |
| Gunther 2006 | 0.31 | [-0.27; 0.88] |
| Brender 1991 | 0.33 | [-0.21; 0.86] |
| Platt 1981 | 0.43 | [-0.36; 1.20] |
| Wilson 1984 | 0.50 | [0.26; 0.75] |
| Troost 2006 | 0.69 | [-0.04; 1.41] |
| Overall effect | 0.04 | [-0.04; 0.12] |

| Executive Function | Hedges' g | 95% CI |
|-------------------|-----------|--------|
| Kwon 2013 | -1.87 | [-2.73; -1.01] |
| Klein 1990 | -0.34 | [-0.93; 0.25] |
| Rapaport 1989 | -0.34 | [-0.93; 0.25] |
| Schlieper 1991 | -0.38 | [-1.26; 0.50] |
| Plait 1984 | -0.06 | [-0.56; 0.42] |
| Platt 1981 | 0.02 | [-0.83; 0.87] |
| Yepe 1977 | 0.03 | [-0.04; 0.71] |
| Robles 2011 | 0.08 | [-0.05; 0.81] |
| de Graaf 2013 | 0.10 | [-0.35; 0.56] |
| Barrickman 1991 | 0.18 | [-0.26; 0.61] |
| Wilson 1984 | 0.23 | [0.00; 0.45] |
| Beers 2005 | 0.25 | [-0.89; 1.38] |
| Seidel 1999 | 0.27 | [-0.36; 0.90] |
| Carlson 1992 | 0.40 | [-0.59; 1.39] |
| Overall effect | -0.01 | [-0.27; 0.24] |

| Intelligence | Hedges' g | 95% CI |
|--------------|-----------|--------|
| Kwon 2013 | -0.91 | [-1.66; -0.16] |
| Plait 1984 | -0.24 | [-1.23; 0.74] |
| Plait 1981 | -0.11 | [-0.54; 0.33] |
| Klein 1990 | -0.06 | [-0.51; 0.39] |
| Chen 2001 | -0.01 | [-0.56; 0.53] |
| Yuan 2018 | 0.03 | [-0.32; 0.38] |
| Eun 2012b | 0.09 | [-0.24; 0.42] |
| Tzirindou 2005 | 0.28 | [0.05; 0.52] |
| Eun 2012a | 0.29 | [-0.02; 0.60] |
| Barrickman 1991 | 0.72 | [0.23; 1.21] |
| Wilson 1984 | 0.86 | [0.00; 1.62] |

| Concept Formation & Reasoning | Hedges' g | 95% CI |
|-------------------------------|-----------|--------|
| Seidel 1999 | 0.08 | [-0.18; 0.33] |
| Seidel 1999 | 0.19 | [-0.14; 0.48] |
| Kwon 2013 | 0.02 | [-0.44; 0.42] |
| Beers 2005 | -0.06 | [-0.54; 0.33] |
| Ferguson 2012 | -0.11 | [-0.54; 0.33] |
| Seidel 1999 | -0.01 | [-0.56; 0.53] |
| Eun 2012b | 0.02 | [-0.44; 0.42] |
| Klein 1990 | -0.03 | [-0.51; 0.18] |
| Tzirindou 2005 | 0.09 | [-0.19; 0.37] |
| Wilson 1984 | 0.27 | [0.04; 0.50] |
| Eun 2012a | 0.30 | [-0.59; 1.28] |
| Overall effect | 0.11 | [-0.07; 0.3] |

| Language | Hedges' g | 95% CI |
|---------|-----------|--------|
| Seidel 1999 | -0.22 | [-0.80; 0.35] |
| Eun 2012b | -0.06 | [-0.44; 0.32] |
| Klein 1990 | -0.03 | [-0.45; 0.42] |
| Tzirindou 2005 | 0.09 | [-0.19; 0.37] |
| Wilson 1984 | 0.27 | [0.04; 0.50] |
| Ferguson 2012 | 0.30 | [-0.59; 1.28] |
| Overall effect | 0.11 | [-0.07; 0.3] |

| Perception | Hedges' g | 95% CI |
|------------|-----------|--------|
| Donati 2007 | -0.05 | [-0.52; 0.42] |
| Robles 2011 | 0.11 | [-0.58; 0.81] |
| Aman 2008 | 0.84 | [0.10; 1.59] |
| Overall effect | 0.28 | [-0.90; 1.38] |
Data availability
All data and code available at https://github.com/ericaghezzi/anticholinergic_med_metaanalysis.

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H.A.D.K. and L.M.E.K. conceptualised the study in consultation with K.R. H.A.D.K. and M.C. wrote the first draft of the manuscript. E.G. carried out the statistical analyses. M.C., T.J.R., D.C., C.S. and J.N.H. carried out the systematic review. All authors provided intellectual input to the manuscript and approved the final version for submission.

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to H.A.D.K.

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