National Institute for Health and Care Excellence

Draft for Consultation

Attention deficit hyperactivity disorder (update)

Appendix 3: Cost-effectiveness analysis: Network meta-analysis for ADHD treatments in combination and individually

NICE guideline CG72

Economic analysis report

September 2017

Draft for Consultation

This guideline was developed by the National Guideline Centre

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1.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles and forest plots in evidence review F on combination treatment) does not help inform which intervention is most effective for managing the symptoms of ADHD. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among the different treatments because there are more than two treatments being compared in the combination review. In addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial.
- There could be conflicting estimates of effect if we try to compare the results of different pairwise comparisons if trying to decide which intervention is best.

An additional problem is that the clinical data needed in a model is dichotomous in nature (because of needing to link to quality of life data), whereas the clinical review focused on continuous outcomes primarily, and therefore to weigh up the costs, benefits and harms of the different interventions additional analysis of the data is needed.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons without breaking randomisation and allows for the ranking of different interventions. In this case the outcomes were defined as:

- probability of response.

These estimates provide a useful clinical summary of the results that can feed into an economic model and facilitate the formation of recommendations based on the best available evidence.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C, and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term “network” better describes the data structure, whereas “mixed treatments” could easily be misinterpreted as referring to combinations of treatments.

1.2 Methods

1.2.1 Study selection

To estimate the probability of response, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical evidence review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular intervention that involves a combination of interventions will be derived only from randomised controlled trials that had that particular combination in a trial arm.

1.2.2 Outcome measures

The guideline clinical evidence reviews considered continuous outcomes to be the priority outcomes that the committee wished to make recommendations from. Dichotomous outcomes were also included but were only extracted from a study into the clinical review if the study didn't report any continuous outcomes. Response to an intervention was the only way to link outcomes to quality of life, and therefore only dichotomous outcomes could be utilised in any modelling.

It would have been difficult to undertake an NMA for the guideline as a whole because of issues with the populations in the studies being dissimilar in terms of medication status, and the differences in the interventions being provided which would have been a particular issue for the non-pharmacological and combination questions. And therefore seeing as the clinical evidence used for the health economic model was already quite far removed from the larger pool of evidence identified for the clinical review (both because of the small pool of evidence being used for treatment effect in the model, and also because the outcomes being used in the model are secondary outcomes on the clinical protocol), this NMA was undertaken by the health economist purely to inform the economic model.

1.2.3 Comparability of interventions

The interventions compared in the model were a subset of those found in the randomised controlled trials included in the clinical evidence review presented in evidence review F: Combination treatment. Studies from the clinical review in the combination question first had to be assessed for whether they reported dichotomous outcomes, which were needed for the model. The comparisons in this pool of relevant studies were then extracted, and as presented in section 1.2 of appendix 2, the rationale for what the comparators were in the NMA were dependent on what comparisons were found in studies with dichotomous outcomes, and whether the committee felt the studies could be pooled or not because of similarity in interventions being assessed.

Treatments included in the network meta-analysis;

- Behavioural therapy
- Atomoxetine
- Combination of behavioural therapy and atomoxetine

1.2.4 Baseline risks

The baseline risk is defined as the risk of achieving the outcome of interest in the baseline treatment arm of the included trials (i.e. the treatment labelled '1'). A meta-analysis was run on the baseline separately to the NMA model.

1.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS[4]. We adapted fixed effects and random effects code from the NICE Decision Support Unit[1] (by adding additional code to calculate the residual deviance for example). This method accounts for the correlation between study level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. A diagram of the evidence network is presented in section 1.3, with the detail of the comparisons in each study in Table 1.

A baseline meta-analysis was undertaken as it is recommended by the NICE Decision Support Unit that the same Generalised Linear Modelling framework is used to model the absolute effects of a "standard treatment" or placebo comparator, as that proposed for synthesis of relative treatment effects. This was informed by two studies, and the code can be found in section 1.6. This used a fixed effects model instead of a random effects model, as there weren't enough studies to estimate the heterogeneity. However, the sample probabilities of the two studies were similar.

Both the baseline meta-analysis and the NMA used a binomial likelihood logit link model. Because we were interested in an outcome of the number of events (responses) out of the total number of patients in each arm in each trial, we assumed that the data generation process follows a Binomial likelihood. Since the parameters of interest were probabilities and therefore can only take values between 0 and 1, a transformation (link function) was used that maps these probabilities into a continuous measure between plus and minus infinity. For a Binomial likelihood the most commonly used link function is the logit link function.

The NMA model used a fixed effects model, with parameters estimated by Markov chain Monte Carlo simulation. Both a random effects and fixed effects model were tested and the goodness of fit was compared. As there wasn't much difference between the two, a fixed effects model was used.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of probability of response, are reported in section 1.3 below.

The aim of the NMA was to calculate the probability of response, for ease of interpretation, and so that they could be easily fed into the economic model.

A key assumption behind an NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics.

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. In this network it is arguable if we need to check for consistency at all since the only loop is formed by a 3-arm study which is consistent by design. However, we tested for inconsistency by fitting an inconsistency model[2] for networks of binary outcomes. We compared the posterior mean of

the residual deviance between the consistency and inconsistency models to see which was a better fit to the data (closest to the number of trial arms in each network) and checked that the difference in deviance information criterion (DIC) values between the two models was small (less than 3-5), or if it was larger, that the smaller DIC and hence better fitting model was the consistency model. We also compared the direct and indirect evidence by testing if the (1,2) and (1,3) comparisons in the 3-arm trial, plus the (1,3) comparison in the 2-arm trial, agree with the (2,3) comparison in the other 2-arm trial. A p-value for inconsistency was also calculated. There was no evidence of inconsistency.

1.3 Results

1.3.1 Included studies

Three[3,5,6] studies were identified as reporting dichotomous outcomes of response that also had relevant comparators (see more on this in the clinical data overview section of appendix 2 (section 1.2).

One study had 3 comparators[3] and was the only study to form a closed loop, with the other two studies having 2 comparators [5,6].

The network can be seen in Figure 1, and the trial data for each of the studies included in the NMA are presented in

Table 1.

Figure 1: Network of studies used for treatment response

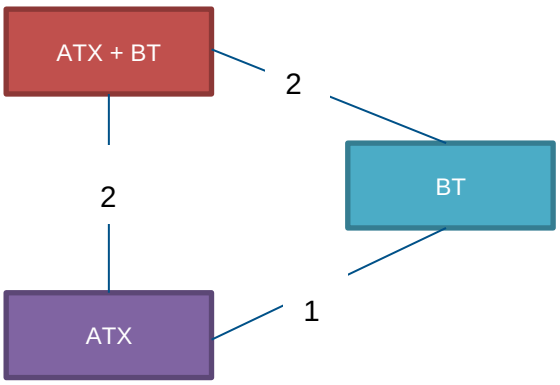

Table 1: Study data for ADHD network meta-analysis

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				N	No. A	N	No. A	N	No. A
Handen 2015	Behavioural therapy	Atomoxetine	Combination	9	31	15	32	15	31
Waxmonsky 2010	Atomoxetine	Combination		14	27	16	29	-	-
Svanborg	Behavioural	Combination		14	50	35	49	-	-

Study	Intervention 1	Intervention 2	Intervention 3	Intervention 1		Intervention 2		Intervention 3	
				N	No. A	N	No. A	N	No. A
2009	therapy								

N: number of events, No.A: number analysed

Table 2 also summarises the studies in more detail.

Table 2: Study detail

Study	Intervention 1	Intervention 2	Intervention 3
Handen 2015 Aged 5-14. Mean age = around 8 in each group. 45.3% had received prior treatment for ADHD.	Behavioural therapy: (parent training plus placebo). Weekly meetings of 60-90 minutes. 9 meetings. A home visit was also conducted between the second and third session. N=31	Atomoxetine (ATX) "Final dose of 49.8mg or 1.3mg/kg. ATX doses were individually adjusted according to a weight-based dosage schedule, with medical clinicians allowed to delay increases or to reduce doses due to AEs. Initial dose = 0.3mg/kg/day (rounded to the nearest 5 mg) with weekly escalations by 0.3mg/kg/day, unless there were limiting side effects or no further room for improvement, to a target dose of 1.2 mg/kg/day, and could be increased to a maximum of 1.8 mg/kg/day based on clinical status and response" N=32	Combination Final dose of 40mg or 1.35mg/kg. Weekly 1:1 meetings of 60-90 minutes. Assumed for 10 weeks? A home visit was also conducted between the second and third session. N=31
Waxmonsky 2010 Aged 6-12. Mean 8.59. Some had previously taken ATX and some had started it before the trial. 37.5% had never taken stimulants. Excluded people who previously failed to respond to ATX.	Atomoxetine Medication provided in a single morning dose. Dose of 0.5mg/kg was started for 3 days then 0.8mg/kg for next 4 days, on day 8 everyone had dose increased to 1.2mg/kg. At 3 weeks tolerability was assessed and dose could be increased to 1.8mg/kg if CGI-S score was 4 or worse. Mean dose at study endpoint was 1.47mg/kg in ATX group. N=27	Combination Medication provided in a single morning dose. Dose of 0.5mg/kg was started for 3 days then 0.8mg/kg for next 4 days, on day 8 everyone had dose increased to 1.2mg/kg. At 3 weeks tolerability was assessed and dose could be increased to 1.8mg/kg if CGI-S score was 4 or worse. Mean dose at study endpoint was 1.40mg/kg in ATX+BT group. 3 components to BT; parenting program, social skills training, and school based daily report card. Sessions were weekly for 2 hrs in groups, children attended a simultaneous social skills program. N=29	
Svanborg 2009	Behavioural therapy	Combination	

Aged 6-15 Mean = 11.5 stimulant naïve children	(placebo + psycho-education) Parents participated in 4 session psycho-educational training. Four 3 hour group sessions. Contains components that might be more behavioural training. N=50	(ATX + psychoeducation) 0.5mg/kg during the first week, thereafter 1.2mg/kg (< or = 70 kg) or 80 mg/day (> 70 kg). It was dispensed at 6 visits (visits 2-7) during active treatment phase. Parents participated in 4 session psycho-educational training. Four 3 hour group sessions. Could be seen as more behavioural therapy as 'the content of the program contained core elements of more comprehensive behavioural treatment programs like parental management training (PMT) and the community parent education program (COPE)'. N=49	

In the NMA, behavioural therapy was chosen to be the baseline treatment that effects would be compared to. There is no 'placebo' comparison of those being compared as all are active treatments. Therefore behavioural therapy was chosen purely because it is the least effective from the data available, and if we had wanted to use ratios from the NMA output (such as odds ratios), then they would be more than 1 when compared to behavioural therapy.Current practice can also vary, and as the populations from the included trials were a mix of people on concurrent treatment or not then it is difficult to make an assumption about what the baseline would be (e.g. if it was newly diagnosed children with moderate impairment then using the last guideline as a guide; behavioural therapy might be the first line option and therefore the baseline). But as this was not the case because of the mixed population, the least effective was chosen.

1.3.2 NMA results

Table 3 summarises the results of the network meta-analysis in terms of the probability of response for each intervention, as well as the standard deviation, median, and confidence interval around each of the probabilities for each intervention.

Table 3: NMA results: Posterior distribution of the probability of response for each intervention

Intervention	Mean	SD	2.50% confidence interval	median	97.50% confidence interval
Behavioural therapy	**0.2842**	0.0501	0.1937	0.2814	0.3899
Atomoxetine	**0.5666**	0.1165	0.3327	0.5703	0.7810
Combination	**0.6250**	0.0950	0.4289	0.6296	0.7964

The probabilities of response were used directly in the model as the clinical outcomes. Quality of life was attached to the responders and non-responders, and also costs of the interventions were included to generate ICERS.

1.3.2.1 Goodness of fit and inconsistency

The fixed effects model used for the NMA was a good fit, with a residual deviance of 7.3 reported. This corresponds well to the total number of trial arms, 7.

An inconsistency model was run and the Deviance Information Criterion (DIC) statistics were as follows in Table 4. The difference in the DIC is small (<3-5) with the consistency model having the lower DIC value. This suggests that it fits the data better than the inconsistency model.

A p-value for inconsistency was also calculated (0.78).

Table 4: Goodness of fit statistics for the network meta-analysis and inconsistency models

	Deviance Information Criterion (DIC)	Posterior mean of the residual deviance (resdev)
Consistency model (fixed effects)	39.818	7.319
Inconsistency model (fixed effects)	41.746	8.256

1.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in evidence review F on combination treatment, deciding upon the most clinical and cost effective intervention in an ADHD population is challenging. In order to overcome the difficulty of interpreting the conclusions from numerous separate comparisons, network meta-analysis of the direct evidence was performed. The findings of the NMA were used to facilitate the guideline committee in decision-making when developing recommendations.

The outcome chosen for the NMA was heavily influenced by the outcome being needed for the health economic model. As previously explained, an NMA for the review as a whole would have been difficult to undertake because of issues with the populations in the studies, and the differences in the interventions being provided. This NMA was undertaken by the health economist purely to inform the economic model.

Our analysis was based on a singular outcome or probability of response. 3 studies informed the ADHD network where 3 different individual or combination treatments were evaluated including a non-pharmacological treatment (behavioural therapy), a pharmacological treatment (atomoxetine), and a combined non-pharmacological and pharmacological intervention (atomoxetine + behavioural therapy).

The NMA was only informed by 3 studies, and therefore was a very small network. However the alternatives would have been either; using the data in the model by crudely working out the response rates through summation across the studies – which would break randomisation. Or choosing one intervention as baseline and applying the relative effect of the others – which can lead to different results depending on which arm was chosen as the baseline, because the different direct comparisons are not identical.Therefore an NMA was the most statistically robust way of combining the data.In the ADHD network, the intervention with the highest probability of response was combination treatment, closely followed by Atomoxetine, and finally behavioural therapy was the least effective (see Table 3). There was a lot of uncertainty about the estimates with the credible intervals for some of the interventions being very wide.

The network seemed to fit well, as demonstrated by DIC and residual deviance statistics. However due to the limited number of studies, the credible intervals around the ranking of treatments in the network was wide, suggesting considerable uncertainty about these results.

1.5 Conclusion

This analysis allowed us to combine findings from different comparisons presented in the review even when direct comparative data was lacking.

For details of the rationale and discussion leading to recommendations, please refer to the section 'the committee's discussion of the evidence' (section 1.11 of evidence review F on combination treatment).

1.6 WinBUGS codes

1.6.1 Winbugs code for the baseline meta-analysis

Atomoxetine baseline Data (BT arm)

==========

2 trials

==========

```
# Binomial likelihood, logit link
# Baseline fixed effects model
model{                          # *** PROGRAM STARTS
for (i in 1:ns){                # LOOP THROUGH STUDIES
    r[i] ~ dbin(p[i],n[i])            # Likelihood
    logit(p[i]) <- m                       # Log-odds of response
#Deviance contribution
    rhat[i] <- p[i] * n[i] # expected value of the numerators
    dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))
          +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
  }
totresdev <- sum(dev[])         # Total Residual Deviance
m ~ dnorm(0,.0001)              # vague prior for mean
logit(R) <- m                   # posterior probability of response
}
```

Data

list(ns=2) # ns=number of studies

r[]	n[]	#	Study ID
9	31	#	1
14	50	#	3

END

Inits

list(m=0)

list(m= -1)

list(m = 1)

1.6.2 Winbugs code for the probability of response

ATX model
treatment 1 = BT
treatment 2 = ATX
treatment 3 = combo

This code is part of
Dias, S., Welton, N.J., Sutton, A.J. & Ades, A.E. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011; last updated September 2016 (available from http://www.nicedsu.org.uk).
This work should be cited whenever the code is used whether in its standard form or adapted.

```
# Binomial likelihood, logit link
# Fixed effects model
model{                              # *** PROGRAM STARTS
for(i in 1:ns){                     # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
    for (k in 1:na[i])  {           # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
# model for linear predictor
        logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]]
# expected value of the numerators
        rhat[i,k] <- p[i,k] * n[i,k]
#Deviance contribution
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
             +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
      }
# summed residual deviance contribution for this trial
    resdev[i] <- sum(dev[i,1:na[i]])
     }
totresdev <- sum(resdev[])      # Total Residual Deviance
d[1]<-0    # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
# obtain all pairwise ORs
for (c in 1:(nt-1)){
    for (k in (c+1):nt)  {
        OR[c,k] <- exp(d[k] - d[c])
        LOR[c,k]<-(d[k]-d[c])
      }
  }
# Provide estimates of treatment effects T[k] on the natural (probability)
scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }
}                                   # *** PROGRAM ENDS
```

Data

# ns= number of studies; nt=number of treatments
list(ns=3, nt=3, meanA=-0.9378, precA=16.11582508)

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
9	31	15	32	15	31	1	2	3	3
14	27	16	29	NA	NA	2	3	NA	2
14	50	35	49	NA	NA	1	3	NA	2

END

Initial Values

#chain 1
list(d=c(NA, 0, 0), mu=c(0, 0, 0))
#chain 2
list(d=c(NA, -1, 0), mu=c(-3, -3, -3))
#chain 3
list(d=c(NA, 2, 0), mu=c(-3, 4, 1))

1.6.3 Winbugs code for NMA inconsistency model

FE model for ATX model data: 3 trials, 3 treatments

==========

1 BT
2 ATX
3 combo

==========

```
# Binomial likelihood, logit link, inconsistency model
# Fixed effects model
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
    mu[i] ~ dnorm(0,.0001)  # vague priors for trial baselines
    for (k in 1:na[i])  {   # LOOP THROUGH ARMS
        r[i,k] ~ dbin(p[i,k],n[i,k])    # binomial likelihood
        logit(p[i,k]) <- mu[i] + d[t[i,1],t[i,k]]  # model for linear
predictor
#Deviance contribution
        rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
        dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
          +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-
rhat[i,k])))
      }
# summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
  }
totresdev <- sum(resdev[])   # Total Residual Deviance
for (k in 1:nt) { d[k,k] <- 0 } # set effects of k vs k to zero
for (c in 1:(nt-1)) {  # priors for all mean treatment effects
    for (k in (c+1):nt)  { d[c,k] ~ dnorm(0,.0001) }
  }
# calculate prob of inconsistency
d.23 <- d[1,3]-d[1,2]
diff.23 <- d.23 - d[2,3]
prob <- step(diff.23)
} # *** PROGRAM ENDS
```

Data

```
# ns= number of studies; nt=number of treatments
list(ns=3, nt=3)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
9	31	15	32	15	31	1	2	3	3
14	27	16	29	NA	NA	2	3	NA	2
14	50	35	49	NA	NA	1	3	NA	2

```
END
```

Inits

```
#chain 1
list(mu=c(-2,0,2),
d = structure(.Data = c(
        NA,0,0,
        NA,NA,0,
                NA, NA, NA),
.Dim = c(3,3))   )

#chain 2
list(mu=c(1,0,3),
d = structure(.Data = c(
        NA,2,2,
        NA,NA,2,
                NA, NA, NA),
.Dim = c(3,3))   )

#chain 3
list(mu=c(2,-2,1),
d = structure(.Data = c(
        NA,1,1,
        NA,NA,1,
                NA, NA, NA),
.Dim = c(3,3))   )
```

References

1. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Medical Decision Making. 2013; 33(5):607-617

2. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Medical Decision Making. 2013; 33(5):641-656

3. Handen BL, Aman MG, Arnold LE, Hyman SL, Tumuluru RV, Lecavalier L et al. Atomoxetine, parent training, and their combination in children with autism spectrum disorder and attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2015; 54(11):905-915

4. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in Medicine. 2004; 23(20):3105-3124

5. Svanborg P, Thernlund G, Gustafsson PA, Hagglof B, Poole L, Kadesjo B. Efficacy and safety of atomoxetine as add-on to psychoeducation in the treatment of attention deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled study in stimulant-naive Swedish children and adolescents. European Child and Adolescent Psychiatry. 2009; 18(4):240-249

6. Waxmonsky JG, Waschbusch DA, Pelham WE, Draganac-Cardona L, Rotella B, Ryan L. Effects of atomoxetine with and without behavior therapy on the school and home functioning of children with attention-deficit/hyperactivity disorder. Journal of Clinical Psychiatry. 2010; 71(11):1535-1551

Appendices

Appendix A: Search strategy

A.1 Clinical search literature search strategy

Searches for patient views were run in Medline (OVID), Embase (OVID), CINAHL, Current Nursing and Allied Health Literature (EBSCO) and PsycINFO (ProQuest). Search filters were applied to the search where appropriate.

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1948 – 28 April 2017	Exclusions Patient views/qualitative studies
Embase (OVID)	1974– 28 April 2017	Exclusions Patient views/qualitative studies
CINAHL (EBSCO)	Inception– 28 April 2017	Exclusions Patient views/qualitative studies
PsycINFO (ProQuest)	Inception– 28 April 2017	Exclusions Patient views/qualitative studies

Medline (Ovid) search terms

1.	"attention deficit and disruptive behavior disorders"/ or attention deficit disorder with hyperactivity/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter/
11.	editorial/
12.	news/
13.	exp historical article/
14.	Anecdotes as Topic/
15.	comment/
16.	case report/
17.	(letter or comment*).ti.
18.	or/10-17

19.	randomized controlled trial/ or random*.ti,ab.
20.	18 not 19
21.	animals/ not humans/
22.	Animals, Laboratory/
23.	exp animal experiment/
24.	exp animal model/
25.	exp Rodentia/
26.	(rat or rats or mouse or mice).ti.
27.	or/20-26
28.	9 not 27
29.	Qualitative research/ or Narration/ or exp Interviews as Topic/ or exp "Surveys and Questionnaires"/ or Health care surveys/
30.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
31.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
32.	or/29-31
33.	28 and 32

1

2 **Embase (Ovid) search terms**

1.	attention deficit disorder/
2.	((attenti* or disrupt*) adj3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*)).ti.
3.	((attenti* or disrupt*) adj3 disorder*).ab.
4.	(adhd or addh or ad hd or ad??hd).ti,ab.
5.	(attenti* adj3 deficit*).ti,ab.
6.	(((hyperkin* or hyper kin*) adj1 (syndrome* or disorder*)) or hkd).ti,ab.
7.	(minimal brain adj2 (dysfunct* or disorder*)).ti,ab.
8.	or/1-7
9.	limit 8 to English language
10.	letter.pt. or letter/
11.	note.pt.
12.	editorial.pt.
13.	case report/ or case study/
14.	(letter or comment*).ti.
15.	or/10-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animal/ not human/
19.	nonhuman/
20.	exp Animal Experiment/
21.	exp Experimental Animal/

22.	animal model/
23.	exp Rodent/
24.	(rat or rats or mouse or mice).ti.
25.	or/17-24
26.	9 not 25
27.	health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/
28.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
29.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
30.	or/27-29
31.	26 and 30

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2 **CINAHL (EBSCO) search terms**

S1.	(MH "Attention Deficit Hyperactivity Disorder")
S2.	((attenti* or disrupt*) n3 (adolescent* or adult* or behav* or child* or class or classes or classroom* or condition* or difficult* or disorder* or learn* or people or person* or poor or problem* or process* or youngster*))
S3.	adhd or addh or ad hd or ad/hd
S4.	attenti* n3 deficit*
S5.	(((hyperkin* or hyper kin*) n1 (syndrome* or disorder*)) or hkd)
S6.	(minimal brain n2 (dysfunct* or disorder*))
S7.	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8.	(MH "Qualitative Studies+")
S9.	(MH "Qualitative Validity+")
S10.	(MH "Interviews+") OR (MH "Focus Groups") OR (MH "Surveys") OR (MH "Questionnaires+")
S11.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*)
S12.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* n3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*)
S13.	S8 OR S9 OR S10 OR S11 OR S12
S14.	S7 AND S13
S15.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S16.	S14 NOT S15 Limiters - English Language; Exclude MEDLINE records

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4 **PsycINFO (ProQuest) search terms**

1.	SU.EXACT.EXPLODE("Attention Deficit Disorder") OR TI((attenti* OR disrupt*) NEAR/3 (adolescent* OR adult* OR behav* OR child* OR class OR classes OR classroom* OR condition* OR difficult* OR disorder* OR learn* OR people OR person* OR poor OR problem* OR process* OR youngster*)) OR AB((attenti* OR disrupt*) NEAR/3 disorder*) OR TI,AB(adhd OR addh OR ad-hd OR ad??hd) OR TI,AB(attenti* NEAR/3 deficit*) OR TI,AB(((hyperkin* OR (hyper-kin*)) NEAR/1 (syndrome* OR disorder*)) OR hkd) OR TI,AB(minimal NEAR/1 brain NEAR/2 (dysfunct* OR disorder*))
2.	SU.EXACT("Qualitative Research") OR (SU.EXACT("Narratives") OR SU.EXACT("Interviews")) OR (SU.EXACT("Questionnaires") OR SU.EXACT.EXPLODE("Surveys")) OR (qualitative OR interview*) OR (focus-group* OR theme*) OR (questionnaire* OR survey*) OR (metasynthes* OR meta-synthes*) OR (metasummar* OR meta-summar*) OR (metastud* OR meta-stud*) OR (metathem* OR meta-them*) OR ethno* OR (emic OR etic) OR (phenomenolog* OR "grounded theory") OR (constant-compar* OR thematic* NEAR/3 analys*) OR (theoretical-sampl* OR purposive-sampl*) OR (hermeneutic* OR heidegger*) OR (husserl* OR colaizzi*) OR (van-kaam* OR van-manen*) OR (giorgi* OR glaser*) OR (strauss* OR ricoeur*) OR (spiegelberg* OR merleau*)
3.	1 AND 2
4.	NOT (Dissertations & Theses AND Books)
5.	English

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