

Attention deficit hyperactivity disorder in children and young people: clonidine

Evidence summary

Published: 2 April 2013

[nice.org.uk/guidance/esuom8](https://www.nice.org.uk/guidance/esuom8)

Key points from the evidence

The content of this evidence summary was up-to-date in April 2013. See [summaries of product characteristics](#) (SPCs), [British national formulary](#) (BNF) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Clonidine is an alpha₂-adrenergic agonist that is licensed in the UK for adults to prevent migraine, prevent hot flushing associated with menopause, and treat hypertension. It does not have a UK licence to treat attention deficit hyperactivity disorder (ADHD) in any age group. It is sometimes used off-label (generally as an add-on to a licensed psychostimulant medicine, such as methylphenidate) to treat ADHD in children and young people under 18 years. This review does not include evidence for the use of extended-release clonidine preparation ([Kapvay](#)), which is approved in the USA for treating ADHD.

NICE has issued a clinical guideline on [Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults](#) (NICE clinical guideline 72). This recommends that in children and young people whose ADHD is unresponsive to methylphenidate, atomoxetine and dexamfetamine, further treatment may include medication unlicensed for ADHD (such as bupropion, clonidine, modafinil and imipramine), but this should only be considered in the context of tertiary services.

One randomised controlled trial (RCT; [CAT study, Palumbo et al. 2008](#)) provided weak evidence that using clonidine as an add-on to methylphenidate for 16 weeks was no better than using methylphenidate alone at treating ADHD symptoms in children and young people.

A second RCT ([Hazell et al. 2003](#)) provided weak evidence that clonidine (added to ongoing treatment with psychostimulants) improved conduct disorder symptoms in children and young people with either ADHD and conduct disorder, or ADHD and oppositional defiant disorder over 6 weeks. However, it did not improve hyperactivity symptoms.

These 2 RCTs were relatively small (n=189 total study population) and short term (6 to 16 weeks of treatment), so did not provide evidence for long-term efficacy and safety.

Adding clonidine to existing stimulant therapy was associated with an increase in moderate to severe side effects, most notably sedation and drowsiness. However, 3 RCTs ([CAT study, Daviss et al. 2008](#), [Hazell et al. 2003](#) and [Tourette's Syndrome Study Group 2002](#)) suggested that this may be an acute effect that reduces over time.

One RCT ([CAT study, Daviss et al. 2008](#)) found a significantly higher incidence of bradycardia in children using clonidine for 16 weeks. One child taking clonidine and methylphenidate was withdrawn from this study because of asymptomatic heart abnormalities detected by electrocardiogram (ECG).

Because of the small and short-term nature of the RCTs identified, additional serious adverse events due to clonidine cannot be ruled out. Children and young people with serious existing cardiac problems were generally excluded from the RCTs and may be more at risk of serious side effects. The NICE clinical guideline on [ADHD](#) recommends that a cardiovascular examination and ECG should be carried out before starting treatment with clonidine in children or young people with ADHD.

One further RCT ([Tourette's Syndrome Study Group 2002](#)) found that clonidine monotherapy, methylphenidate monotherapy, and combination therapy with clonidine and methylphenidate were all significantly more effective than placebo in treating ADHD symptoms and tic symptoms in children and young people with ADHD and either Tourette's syndrome or other tic disorders.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Clonidine is sometimes used off-label, generally in combination with a psychostimulant, to treat attention deficit hyperactivity disorder (ADHD) in children and young people under 18 years in the UK.

Regulatory status of clonidine

Clonidine is not currently licensed in the UK for the treatment of ADHD in adults or children and young people under 18 years.

Clonidine hydrochloride 25 microgram tablets (available from [generic](#) manufacturers, [Sandoz Limited](#), or from Boehringer Ingelheim Limited as [Dixarit](#)) are currently licensed in the UK to prevent migraine and similar types of recurrent vascular headache, and to prevent hot flushes associated with menopause in women. They are not generally recommended for children under 12 or 18 years, depending on the individual licence.

Clonidine hydrochloride 100 microgram tablets ([Catapres](#), Boehringer Ingelheim Limited) are also licensed in the UK for all grades of essential and secondary hypertension in adults. The [summary of product characteristics](#) states that the efficacy of clonidine has been investigated in a few clinical trials with paediatric patients with ADHD, Tourette's syndrome and stuttering, but the efficacy of clonidine in these conditions has not been demonstrated. Therefore, it states that the use of clonidine is not recommended in children and young people under 18 years.

In 2010, the [US Food and Drug Administration](#) approved extended-release clonidine hydrochloride 100 microgram and 200 microgram tablets ([Kapvay](#), Shionogi Inc) for use in the USA as monotherapy, and as an add-on to a psychostimulant, to treat ADHD in children and young people aged 6–17 years. However, this medicine is not licensed for any use in the UK.

The use of standard-release clonidine hydrochloride tablets available in the UK to treat ADHD symptoms in children, young people or adults would be off-label, whereas the use of the extended-release tablets would be unlicensed.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using clonidine outside its authorised indications.

Evidence statements

- Evidence from 1 randomised controlled trial (RCT; [CAT study, Palumbo et al. 2008](#)) provided weak evidence that using clonidine as an add-on to methylphenidate was no better than methylphenidate alone at treating ADHD symptoms in children and young people.
- Evidence from 1 RCT ([Hazell et al. 2003](#)) provided weak evidence that clonidine improved conduct disorder symptoms in children and young people with ADHD and either conduct disorder or oppositional defiant disorder, compared with placebo (both added to ongoing treatment with psychostimulants). However, it did not improve hyperactivity symptoms.
- These 2 RCTs were relatively small (n=189 total study population) and short term (6 to 16 weeks of treatment) so did not provide evidence for long-term efficacy and safety.
- Evidence from 1 RCT ([CAT study, Daviss et al. 2008](#)) indicates that clonidine (alone or in combination with methylphenidate) is associated with significantly more moderate and severe side effects than methylphenidate alone or placebo, particularly sedation and drowsiness. Despite this, clonidine appeared well tolerated and was not associated with differences in treatment withdrawal.
- Three RCTs ([CAT study, Daviss et al. 2008](#), [Hazell et al. 2003](#) and [Tourette's Syndrome Study Group 2002](#)) reported that sedation or drowsiness due to clonidine reduced over time to levels similar to those in children and young people not taking it.
- One RCT ([CAT study, Daviss et al. 2008](#)) found clonidine use (alone or in combination with methylphenidate) in children with ADHD was associated with a higher incidence of

bradycardia. One child in the clonidine plus methylphenidate group was withdrawn from this study because of abnormal electrocardiogram (ECG) findings.

- Other serious adverse events due to clonidine treatment cannot be ruled out because of the small and short-term nature of the RCTs identified. Similarly, the RCTs excluded children and young people with existing serious cardiac problems, so risks in this group are unknown and may be higher than those reported in the RCTs.
- One RCT ([Tourette's Syndrome Study Group 2002](#)) showed that using clonidine with methylphenidate improved ADHD symptoms and tic symptoms in children and young people with ADHD and Tourette's syndrome or other tic disorders compared with placebo.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

Efficacy

Two RCTs ([Hazell et al. 2003](#), n=67 and [Palumbo et al. 2008, CAT study](#), n=122) were identified that assessed clonidine for treating ADHD in children and young people either alone or in combination with a stimulant. In both RCTs, the extent to which previous stimulant treatment had failed to control ADHD symptoms before enrolment in the trials, or the extent to which stimulants had been optimised before enrolment, were not clear. Both trials were relatively small, meaning that small clinical effects could be missed; and short term (treatment periods 6 to 16 weeks), meaning any observed benefits may be temporary.

Together, they provide weak evidence that using clonidine as an add-on therapy to stimulant medication does not improve ADHD symptom scores overall compared with using a stimulant alone, but may improve conduct disorder symptom scores in children with both ADHD and conduct disorder.

Variations in how ADHD symptoms were measured, treatment durations, stimulant treatment optimisation, ADHD subtypes and ADHD comorbidities, could all potentially influence whether or not a treatment effect was found in the studies.

Children and young people with ADHD

In children and young people with ADHD who also had conduct or oppositional defiant disorder, [Hazell et al. \(2003\)](#) found a benefit of using clonidine add-on therapy specifically to improve conduct disorder.

[Hazell et al. \(2003\)](#) indicated that, compared with placebo, adding clonidine syrup (100–200 micrograms/day) to ongoing stimulant therapy (methylphenidate or dexamfetamine used previously for a minimum of 3 months) significantly improved the proportion of children and young people with ADHD and either conduct or oppositional defiant disorder who were 'responders' on the conduct subscale of the parent-reported Conners behaviour checklist after 6 weeks treatment (see table 1). The absolute difference in the proportion of children and young people who were 'responders' to clonidine, compared with placebo, in addition to their ongoing stimulant therapy was 36.1%. This meant a number needed to treat (NNT) of around 3; that is, 3 children or young people would need to be treated with clonidine in addition to stimulant to obtain 1 extra 'responder' on this subscale over 6 weeks. However, no significant difference was found between the groups for the proportion of children and young people who were 'responders' on the hyperactive index subscale. Although blinded at randomisation, this study was effectively 'unblinded' as most of the parents guessed the treatment allocation, possibly because of the sedative effects of clonidine in the early stages of the trial. This may have biased the results in favour of clonidine being effective.

[Palumbo et al. \(2008; CAT study\)](#) found no benefit of clonidine on the primary ADHD symptom outcomes measured in a more mixed ADHD population. The study recruited children with any ADHD subtype but excluded comorbid tic disorders and other major medical disorders that would affect safe use of the study drug. The results of treatment in children with ADHD and conduct or oppositional defiant disorder were not discussed separately in the published results.

[Palumbo et al. \(2008\)](#) found no statistically significant improvements in ADHD symptoms in children given clonidine plus methylphenidate compared with methylphenidate alone over 16 weeks using the Conners abbreviated symptom questionnaire for teachers (ASQ-T; primary outcome) or other secondary outcome rating scales (see [table 2](#)).

The same study grouped children receiving clonidine (alone or in combination with methylphenidate) and those not receiving clonidine (methylphenidate alone or placebo) and found there was no statistically significant difference in improvements in ADHD symptoms on the primary outcome (the ASQ-T). However, statistically significant improvements were seen with

clonidine in ADHD symptoms assessed by the ASQ-parent version and the Children's global assessment scale (secondary outcomes).

Children and young people with ADHD and Tourette's syndrome

One RCT in children and young people with ADHD and Tourette's syndrome or chronic tic disorder ([Tourette's Syndrome Study Group 2002](#)) showed clonidine alone, methylphenidate alone, or both drugs together, were beneficial for ADHD symptoms over 16 weeks treatment. All achieved a statistically significant improvement compared with placebo for the primary outcome of change in ASQ-T baseline to 16 weeks. Whilst some patients did report worsening of tics as an adverse event in each of the study treatment groups, analysis of the results overall showed that using clonidine alone, methylphenidate alone or both drugs together improved tic symptoms statistically significantly more than using placebo.

Table 1 Summary of the trial: [Hazell et al. \(2003\)](#)

	Placebo + ongoing stimulant ^a	Clonidine + ongoing stimulant ^a	Analysis
Randomised	n=29	n=38	
Efficacy (ITT, LOCF)	n=29	n=37 ^b	
Co-primary outcome: Responders CBC-P Conduct subscale	20.7% (6/29)	56.8%(21/37)	Responders: number achieving 38% reduction from baseline to 6 weeks Absolute difference 36.1%, p<0.01 NNT=3 over 6 weeks to get 1 extra conduct scale responder
Co-primary outcome: Responders CBC-P Hyperactive Index subscale	17.2% (5/29)	35.1% (13/37)	Responders: number achieving 43% reduction from baseline to 6 weeks NS, p=0.16
Safety	n=unclear	n=unclear	

Parent-report side effect rating scale	Not reported	Not reported	Greater reduction in side effects for clonidine group overall (linear trend $p < 0.05$). 2 side effects: 'dizziness' and 'drowsiness' were higher in clonidine group ($p < 0.05$); effects transient, resolved by week 6
Child-report side effect rating scale	Not reported	Not reported	Greater reduction in side effects for clonidine group overall (linear trend $p < 0.05$).
<p>Abbreviations: CBC-P, Conners behaviour checklist parent-report; <u>ITT</u>, intention to treat; LOCF, last observation carried forward; n, number of patients; NS, not statistically significant; <u>NNT</u>, number needed to treat; p, p value.</p> <p>^a Stimulants used: methylphenidate or dexamfetamine.</p> <p>^b There was no parent-reported data for 1 child, so results are presented for 37 (not 38) children in the clonidine group.</p>			

Table 2 Summary of the trial: CAT study; *Palumbo et al. (2008)* and *Daviss et al. (2008)*

	Placebo	Methylphenidate monotherapy	Clonidine monotherapy	Methylphenidate + clonidine	Analysis
Randomised	n=30	n=29	n=31	n=32	
Efficacy (ITT, LOCF)	n=30	n=29	n=31	n=32	
Primary outcome: Mean change from baseline to 16 weeks ASQ-T	-3.20 points (SD 6.38)	-5.07 points (SD 6.79)	-3.35 points (SD 5.78)	-7.28 points (SD 7.91)	NS treatment effect methylphenidate + clonidine versus methylphenidate = -1.9 (95% CI -4.9 to 1.2) $p=0.23$

Selected secondary outcomes:					
Mean change from baseline to 16 weeks ASQ-P	Not reported	Not reported	Not reported	Not reported	NS treatment effect methylphenidate + clonidine versus methylphenidate = -3.0 (95% CI -6.4 to 0.4) p=0.08
Mean change from baseline to 16 weeks CGAS	Not reported	Not reported	Not reported	Not reported	NS treatment effect methylphenidate + clonidine versus methylphenidate = 2.7 (95% CI -2.6 to 8.1) p=0.32
Safety	n=30	n=29	n=31	n=32	Paper reports differences between taking clonidine (n=63 ^a) and not taking clonidine (n=59 ^b). Only selected significant differences reported below

Any adverse events	40.0%	58.6%	83.9%	75.0%	Taking clonidine 79.4% versus not taking clonidine 49.2%, p=0.0006 absolute difference 30.2% NNH=3
Somnolence	6.7%	6.9%	41.9%	34.4%	Taking clonidine 38.1% versus not taking clonidine 6.8% p<0.0001 absolute difference 31.3% NNH=3
Fatigue	10.0%	0.0%	22.6%	15.6%	Taking clonidine 19.0% versus not taking clonidine 5.1% p=0.03 absolute difference 13.9% NNH=7
Bradycardia (heart rate <60 bpm)	3.3%	3.5%	22.6%	12.5%	Taking clonidine 17.5% versus not taking clonidine 3.4% p=0.02 absolute difference 14.1% NNH=7
Moderate or severe adverse events					

Dull/tired/ listless (parent rating)	3.3%	6.9%	58.1%	37.5%	Significantly higher in those taking clonidine versus not taking clonidine ($p < 0.0001$)
Dull/tired/ listless (teacher rating)	13.3%	6.9%	58.1%	31.3%	Significantly higher in those taking clonidine versus not taking clonidine ($p < 0.0001$)
Sedation/ drowsiness (parent rating)	3.3%	0.0%	54.8%	28.1%	Significantly higher in those taking clonidine versus not taking clonidine ($p < 0.0001$)
Sedation/ drowsiness (teacher rating)	0.0%	0.0%	41.9%	21.9%	Significantly higher in those taking clonidine versus not taking clonidine ($p < 0.0001$)

Abbreviations: ASQ-P, Conners abbreviated symptom questionnaire for parents; ASQ-T, Conners abbreviated symptom questionnaire for teachers; CGAS, Children's global assessment scale; CI, confidence interval; ITT, intention to treat; LOCF, last observation carried forward; n, number of patients; NS, not statistically significant; NNH, number needed to harm; SD, standard deviation.

^a Clonidine monotherapy or in combination with methylphenidate.

^b Placebo or methylphenidate monotherapy.

Safety

Daviss et al. (2008; CAT study) found using clonidine (alone or in combination with methylphenidate) for 16 weeks increased moderate and severe side effects compared with using

placebo or methylphenidate alone (see [table 2](#)). One child was withdrawn from the study while using clonidine alone because of sedation and social withdrawal. However, the majority of children and parents or carers appeared to tolerate side effects (mainly sedation and drowsiness, along with related side effects of dullness, tiredness and listlessness) because there was no corresponding increase in treatment withdrawal in those using clonidine.

A study using a shorter 6-week treatment period ([Hazell et al. 2003](#)) found adding clonidine to ongoing psychostimulant treatment reduced reported side effects compared to ongoing psychostimulant plus placebo (see [table 1](#)).

In [Daviss et al. \(2008; CAT study\)](#), clonidine treatment was associated with an increase in bradycardia. One child withdrew from the study after 14 weeks of treatment (with clonidine plus methylphenidate) because of a prolonged corrected QT interval and an ECG indicating suspected ventricular hypertrophy.

Serious adverse events, including cardiac problems, due to clonidine treatment (alone or in combination with a stimulant) cannot be ruled out given the small and short-term nature of the RCTs reviewed. Children with existing cardiac problems were excluded from the larger studies reporting safety outcomes, so there may be added risks associated with treatment in this subgroup that are unknown.

Cost effectiveness and cost

No cost-effectiveness studies were identified that assessed the use of clonidine in children or young people with ADHD compared with other treatments or no treatment. No estimate of the current use of clonidine to treat ADHD in UK clinical practice was identified.

[NHS electronic drug tariff \(March 2013\)](#) shows that a 100-pack of clonidine 100 microgram tablets (Catapres) costs £5.32; 112-pack of clonidine 25 microgram tablets (generic) costs £4.59.

Relevance to NICE guidance programmes

The use of clonidine in attention deficit hyperactivity disorder (ADHD) is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

[Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults](#) (NICE clinical guideline 72) recommends that in children and young people

whose ADHD is unresponsive to methylphenidate, atomoxetine and dexamfetamine, further treatment may include medication unlicensed for ADHD (such as bupropion, clonidine, modafinil and imipramine), but this should only be considered in the context of tertiary services (see [Alternative treatment options](#) for details).

Intervention and alternatives

Clonidine is an α_2 -adrenergic agonist that is thought to work in people with attention deficit hyperactivity disorder (ADHD) by affecting noradrenaline transmission in the frontal cortex of the brain.

Condition

ADHD is a heterogeneous behavioural syndrome characterised by symptoms of hyperactivity, impulsivity and inattention. Symptoms of ADHD are distributed throughout the population and vary in severity; only those with significant impairment meet criteria for a diagnosis of ADHD. Common coexisting conditions in children and young people with ADHD are disorders of mood, conduct, learning, motor control and communication, and anxiety disorders. As a result, ADHD is sometimes considered as a set of symptoms. The [full version of the NICE clinical guideline on ADHD](#) describes how ADHD is categorically diagnosed using either the International Classification of Diseases, 10th revision (ICD-10) or Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR). ADHD is also reported to affect a significant proportion of children with Tourette's syndrome and other chronic tic disorders ([Tourette's Syndrome Study Group 2002](#)).

Alternative treatment options

The NICE clinical guideline on [ADHD](#) states that parent-training/education programmes are the first-line treatment for parents or carers of pre-school children with ADHD, or parents or carers of children and young people of school age with ADHD and moderate impairment. In school-age children or young people, this can also include group or individual psychological treatment such as cognitive behavioural therapy and/or social skills training.

Drug treatment is not recommended for pre-school children with ADHD. Drug treatment is also not indicated as the first-line treatment for all school-age children and young people with ADHD. It should be reserved for children and young people with severe symptoms and impairment or for those with moderate levels of impairment who have refused non-drug interventions, or whose symptoms have not responded sufficiently to parent-training/education programmes or group

psychological treatment. In school-age children and young people with severe ADHD, drug treatment should be offered as the first-line treatment. Parents should also be offered a group-based parent training/education programme.

If drug treatment is considered appropriate, the NICE clinical guideline on [ADHD](#) states that, depending on a range of factors such as the presence of coexisting conditions, side effects and patient preference, the child or young person may be offered methylphenidate, atomoxetine or dexamfetamine within their licensed indications for managing their ADHD. Specifically, healthcare professionals should consider:

- methylphenidate for ADHD without significant comorbidity
- methylphenidate for ADHD with comorbid conduct disorder
- methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present
- atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate.

If there has been a poor response to parent-training/education programmes, psychological treatment and drug treatment with methylphenidate and atomoxetine, then a comprehensive review is needed. The following are further options for treatment: using higher doses of methylphenidate or atomoxetine; switching to dexamfetamine; further alternative psychological treatments; or referral to regional specialists for alternative drug treatment.

Dexamfetamine should be considered in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine.

In children and young people whose ADHD is unresponsive to methylphenidate, atomoxetine and dexamfetamine, further treatment should only follow after referral to tertiary services. Further treatment may include using medication unlicensed for the treatment of ADHD (such as bupropion, clonidine, modafinil and imipramine) or combining treatments (including psychological treatments for the parent or carer and the child or young person). NICE recommends that the use of medication unlicensed for ADHD should only be considered in the context of tertiary services.

The guideline stipulates that a cardiovascular examination and an electrocardiogram (ECG) should be carried out before starting treatment with clonidine in children or young people with ADHD.

Evidence review: efficacy

Randomised controlled trials for clonidine in children and young people with ADHD

A randomised controlled trial (RCT) by Hazell et al. (2003) randomised 67 children and young people (91% male) with attention deficit hyperactivity disorder (ADHD) aged 6–14 years to receive either clonidine syrup (100–200 micrograms/day, n=38) or placebo (n=29) for 6 weeks as an add-on therapy to ongoing treatment with psychostimulants. Only children and young people with ADHD and either oppositional defiant disorder or conduct disorder who had received treatment for a minimum of 3 months with either methylphenidate or dexamfetamine were eligible to participate. Of the 35 children and young people still being treated with clonidine at the end of the study, 25 were receiving 200 micrograms/day, 6 were receiving 100 micrograms/day and 4 were taking 150 micrograms/day.

A higher proportion of children and young people given clonidine add-on therapy were 'responders' on the conduct subscale of the parent-reported Conners behaviour checklist (co-primary outcome) compared with placebo (56.8% [21 of 37] compared with 20.7% [6 of 29], $p < 0.01$). That is, they reduced their scores on the conduct subscale by 38% from baseline, considered by the authors to represent a clinically significant level of improvement. The absolute difference between the proportion of children and young people who were 'responders' in the clonidine group and the placebo group was 36.1%, giving a number needed to treat (NNT) of 3. This means that approximately 3 children or young people would need to be treated to achieve 1 extra conduct scale 'responder' over the 6-week period. Both placebo and clonidine groups improved over 6 weeks, with clear differences only emerging after 5 and 6 weeks of treatment. For the other primary outcome, the proportion of 'responders' on the hyperactive index subscale of the parent-reported Conners behaviour checklist (those who reduced their scores on the hyperactivity subscale by 43% from baseline, considered by the authors to represent a clinically significant level of improvement), there was no difference between groups (35.1% [13 of 37] with clonidine compared with 17.2% [5 of 29] with placebo, $p = 0.16$). See table 1 for further details.

An RCT by Palumbo et al. (2008; CAT study) randomised 122 children (80.3% male) aged 7–12 years with any subtype of ADHD to receive methylphenidate, clonidine, methylphenidate plus clonidine, or placebo, for 16 weeks.

Two successive 4-week titration periods (4 weeks clonidine, 4 weeks methylphenidate, or matching placebo) were adjusted to optimum doses and then continued for 8 weeks. Mean end-of-study doses were 30.2 ± 18.9 mg/day for methylphenidate, 240 ± 110 micrograms/day for clonidine, and

25.4±18.2 mg/day methylphenidate and 230±130 micrograms/day clonidine in the combination group.

For the primary outcome (change in Conners abbreviated symptom questionnaire for teachers [ASQ-T], baseline to week 16), there was no statistically significant difference between children randomly assigned to methylphenidate plus clonidine (n=32, mean change -7.28, standard deviation [SD] 7.91) and those taking methylphenidate alone (n=29, mean change -5.07, SD 6.79; treatment effect -1.9; 95% [confidence interval] CI -4.9 to 1.2, p=0.23). The treatment effects of methylphenidate plus clonidine compared with methylphenidate alone were also not statistically significantly different when assessed by Conners abbreviated symptom questionnaire for parents (ASQ-P) and Children's global assessment scale (CGAS; both secondary outcomes). See [table 2](#) for further details.

Children receiving methylphenidate (alone or in combination with clonidine) performed better than those not receiving methylphenidate (clonidine alone or placebo) on ASQ-T (treatment effect -2.9, 95% CI -5.1 to -0.8, p=0.008). Whereas the treatment effect in children receiving clonidine (alone or in combination with methylphenidate) compared with those not receiving clonidine (methylphenidate alone or placebo) was not statistically significant on this rating scale (-1.4, 95% CI -3.6 to 0.7, p=0.19).

With regard to secondary outcomes, the rating scales used yielded different results than those obtained using the ASQ-T. Children receiving clonidine (alone or in combination with methylphenidate) were found to have statistically significant improvements in ADHD symptoms (baseline to week 16) compared with those not receiving it when assessed by ASQ-P (p=0.003) and CGAS (p=0.0002). By contrast, ADHD symptoms were not statistically significantly improved in those receiving methylphenidate (alone or in combination with clonidine) compared with those who were not when assessed by CGAS (p=0.06) and ASQ-P (p=0.31).

Using data from the CAT study, [Cannon et al. \(2009\)](#) found there was no statistically significant difference in any of the 4 arms of the trial for 2 measures of quality of life (Daily hassles scale [DHS] and Impact on family scale [IFS]) over the 16-week treatment period. When comparing any drug treatment (methylphenidate alone, clonidine alone, or methylphenidate and clonidine in combination) with placebo, in a post hoc analysis, the study found that treatment statistically significantly improved quality of life for both measures. However, the benefits were modest. DHS score improved by a mean 0.42 points (17.7%) using active treatment compared with 0.07 (2.9%) for placebo (p=0.016), whereas IFS improved 0.45 points (22.3%) on treatment and got worse by 0.03 points (-1.4%) on placebo (p=0.029).

Evidence for clonidine in children and young people with ADHD and comorbid tic disorders

Cochrane review

A systematic review by [Pringsheim et al. \(2011\)](#) looked at drug treatment for ADHD in children and young people with comorbid tic disorders. Two RCTs were identified ([Tourette's Syndrome Study Group 2002](#) and [Singer et al. 1995](#)) that included a clonidine treatment arm. These are described briefly below.

Randomised controlled trials

In a similar design to [Palumbo et al. \(2008; CAT study\)](#), an RCT by [Tourette's Syndrome Study Group \(2002\)](#) randomised 136 children and young people (aged 7–14 years) with ADHD and chronic tic disorder to methylphenidate, clonidine, methylphenidate plus clonidine, or placebo, for 16 weeks. Most children were male (73–92% male depending on the treatment group). Doses were titrated and averaged 250 micrograms/day for clonidine alone and 25.7 mg/day for methylphenidate alone. In the combination group, the clonidine dose averaged 280 micrograms/day and the methylphenidate dose was 26.1 mg/day.

For the primary outcome (change in ASQ-T, baseline to week 16), statistically significant improvements over placebo were seen for clonidine alone (treatment effect 3.3, 98.3% CI –0.2 to 6.8, $p=0.02$), methylphenidate alone (treatment effect 3.3, 98.3% CI –0.2 to 6.8, $p=0.02$) and clonidine plus methylphenidate (treatment effect 6.3, 98.3% CI 2.8 to 9.8, $p<0.0001$).

The main secondary outcome, Yale global tic severity scale (YGTSS) scores, also showed statistically significant improvements over placebo with clonidine alone (treatment effect 10.9, 98.3% CI 2.1 to 19.7, $p=0.003$), methylphenidate alone (treatment effect 9.4, 98.3% CI 0.7 to 18.1, $p=0.01$) and clonidine plus methylphenidate (treatment effect 11.0, 98.3% CI 2.1 to 19.8, $p=0.003$). There were no reported statistical analyses comparing methylphenidate plus clonidine with methylphenidate alone for these end points.

In a 3-arm crossover trial, [Singer et al. \(1995\)](#) randomised 37 children (aged 7–13 years) with ADHD and Tourette's syndrome to receive clonidine (50 micrograms 4 times daily), desipramine (25 mg 4 times daily) or placebo monotherapy for 6 weeks in succession, with 1 week tapering down and 1 week washout periods between treatments. This study had many limitations, including only reporting data for scales showing significant changes, not specifying a primary outcome, and confounding by drug order interactions (the same drug producing different results depending on the order it is introduced). When describing this study, the [Cochrane review](#) concluded that

clonidine did not show a significant difference compared with either placebo or desipramine on any of the outcome measures of ADHD and tic severity, with the exception of 1 subscale in 1 subgroup.

Evidence review: safety

The most consistently reported adverse events associated with clonidine treatment identified from the randomised controlled trials (RCTs) were sedation and drowsiness, along with related side effects of dullness, tiredness and listlessness. [Daviss et al. \(2008\)](#) (reporting safety outcomes of the CAT study) and [Hazell et al. \(2003\)](#) both indicated that the sedation effect was mainly a temporary occurrence in the first few weeks of the study, reducing or resolving 6–8 weeks into treatment. This was also noted in [Tourette's Syndrome Study Group \(2002\)](#).

[Daviss et al. \(2008\)](#) reported that moderate or severe adverse events were more common in children receiving clonidine (alone or in combination with methylphenidate) compared with children receiving methylphenidate alone or placebo (79.4% compared with 49.2%, $p=0.0006$, absolute risk difference 30.2%, number needed to harm [NNH]=3), but this was not associated with higher rates of study withdrawal. Moderate to severe adverse events leading to study withdrawal were cited in 8 of 122 children in the trial, although not always as the primary reason (5 taking clonidine plus methylphenidate, 2 taking clonidine only and 1 taking methylphenidate only). One child was withdrawn from the study while using clonidine alone (200 micrograms/day) because of sedation and social withdrawal.

The prevalence of these side effects (notably sedation) appeared to be less common when clonidine was used in combination with methylphenidate, rather than alone, although no statistical testing was performed for this comparison (see [table 2](#) for details).

Trial completion rates were significantly higher in children receiving clonidine (alone or in combination) compared with those receiving methylphenidate alone or placebo (79.4% compared with 44.1%, $p<0.0001$).

[Hazell et al. \(2003\)](#) reported a significantly greater reduction in parent- and children-reported side effects (assessed through a rating scale) in children and young people using clonidine plus psychostimulant compared with placebo plus psychostimulant over a 6-week treatment period. The only 2 side effects to occur more in the clonidine arm (parent-reported drowsiness and dizziness) were described as transient and resolved by the end of the 6-week treatment period. No serious adverse events or withdrawals because of adverse events were reported in the clonidine arm.

In [Tourette's Syndrome Study Group \(2002\)](#), sedation was a common side effect in those receiving clonidine (alone or in combination with methylphenidate); 48% reported sedation, with 28% rating it as moderate to severe. This compared with 14% reporting sedation in the methylphenidate only group, and 6% in the placebo group, with 8% and 6% of children and young people rating the sedation as moderate or severe respectively (no p values reported). Moderate to severe sedation was reported less in children using clonidine plus methylphenidate (21%) than in those using clonidine alone (35%), but again no p values were reported.

Specific side effects of treatment were not reported in [Singer et al. \(1995\)](#). The authors reported 44.1% (15 of 34) of children experienced at least 1 drug-related problem during placebo treatment, compared with 76.5% (26 of 34) during desipramine treatment and 82.4% (28 of 34) during clonidine treatment.

Cardiovascular side effects

Concerns have been raised about the relative safety of clonidine, particularly in relation to adverse cardiovascular events after isolated reports of sudden death in children treated with clonidine ([Cantwell et al. 1997](#)).

[Daviss et al. \(2008\)](#) reported safety, cardiovascular and vital signs outcomes during the 16-week CAT study. One child receiving clonidine (200 micrograms/day) in combination with methylphenidate (5 mg/day) was withdrawn at week 14 on the recommendation of the study cardiologist after experiencing a prolonged corrected QT interval (>440 ms) as well as electrocardiogram (ECG) findings suggestive of left ventricular hypertrophy. They had no reported cardiac symptoms and a normal echocardiogram.

A higher proportion of children taking clonidine (alone or in combination with methylphenidate), had bradycardia (heart rate less than 60 bpm) compared with those receiving methylphenidate alone or placebo (17.5% compared with 3.4%, $p=0.02$, absolute difference 14.1%, NNH=7). The authors highlighted a non-significant difference showing children taking clonidine exhibited a greater mean decrease in heart rate over the 16-week study period (-4.1 standard deviation [SD] 13.4) compared with those not receiving clonidine (-0.7 SD 8.8, $p=0.09$). No other significant differences between treatments were observed for other ECG or vital sign measures at 16 weeks.

Importantly, children with known serious cardiac problems or abnormal ECG at baseline were excluded from this study, so the safety of clonidine alone or in combination with methylphenidate in children with existing cardiac problems cannot be established from this study.

Children and young people with known serious cardiac problems or abnormal ECG at baseline were also excluded from the [Tourette's Syndrome Study Group \(2002\)](#). One child in the combination group of this study was withdrawn at week 4 because of asymptomatic isorhythmic AV dissociation detected on ECG. However, the authors reported no overall evidence of cardiac toxicity by ECG monitoring.

Cardiovascular function was assessed through blood pressure and pulse recordings in [Hazell et al. \(2003\)](#). ECGs were not recorded.

Effect on tic disorders

In [Tourette's Syndrome Study Group \(2002\)](#), 20% of children and young people treated with methylphenidate (alone or in combination with clonidine) reported worsening of tics as an adverse event. This compared with 26% taking clonidine alone and 22% receiving placebo (no p values reported). Tics were reported to limit further dose increases in children and young people more often in those assigned methylphenidate alone (35%) than methylphenidate plus clonidine (15%), clonidine alone (18%) or placebo (19%) (no p values reported). Compared with placebo, tic severity (assessed by Yale global tic severity scale [YGTSS] and other tic rating scales) decreased in all the active treatment groups over the course of the 16-week trial.

Evidence review: economic issues

Cost effectiveness

No cost-effectiveness studies were identified that assessed the use of clonidine therapy in children and young people with attention deficit hyperactivity disorder (ADHD) compared with other treatments or no treatment.

We were not able to construct a simple model comparing the cost of using clonidine to treat ADHD relative, or in addition, to other treatments because of a lack of relevant data. Key missing information included current use of clonidine, typical treatment dose and typical treatment duration.

Cost

[NHS electronic drug tariff \(March 2013\)](#) shows that a 100-pack of clonidine 100 microgram tablets (Catapres) costs £5.32, 112-pack of clonidine 25 microgram tablets (generic) costs £4.59.

The typical treatment dose for clonidine in ADHD is not known. However, in [Hazell et al. \(2003\)](#), most children and young people were taking 200 micrograms/day; in [Palumbo et al. \(2008\)](#), doses averaged 230–240 micrograms/day; and in [Tourette's Syndrome Study Group \(2002\)](#), doses averaged 250–280 micrograms/day.

Current drug usage

No information on current use of clonidine for ADHD was available at the time this evidence summary was prepared.

Evidence strengths and limitations

The evidence identified had the following limitations.

There was variation in the length of clonidine treatment ranging from 6 weeks ([Hazell et al. 2003](#)) to 16 weeks ([Palumbo et al. 2008](#) and [Tourette's Syndrome Study Group 2002](#)). The review by [Pringsheim et al. \(2011\)](#) suggested that clinical response to clonidine can take several months and so a difference in treatment time of 10 weeks is likely to be clinically significant.

The short treatment periods used in the studies (6–16 weeks) leave open the possibility that any treatment effects may be temporary and longer-term adverse events may be missed. Similarly, the randomised controlled trials (RCTs) identified had relatively small patient numbers, meaning that only large differences in treatment effects would be detected. Smaller, but clinically significant, differences may have been missed.

Drop-out rates were also an issue, particularly in [Palumbo et al. \(2008\)](#) where only 78 out of 122 children (63.9%) completed the trial. This trial reported relatively high levels of missing data and used last observation carried forward that may have affected the results.

Each trial differed in the way it used clonidine. [Hazell et al. \(2003\)](#) used it only as an add-on to pre-existing stimulant therapy, whereas other trials required any previous treatment to stop and be replaced by clonidine alone or clonidine in combination with methylphenidate ([Palumbo et al. 2008](#) and [Tourette's Syndrome Study Group 2002](#)). In both cases, it was not clear to what extent previous stimulant treatment had failed to control attention deficit hyperactivity disorder (ADHD) symptoms. A common reason for declining participation in the [Hazell et al. \(2003\)](#) trial was a perception by parents that ADHD symptoms were adequately controlled by stimulants alone. Over 40% of children in each trial arm of [Palumbo et al. \(2008\)](#) had used stimulants previously (range 40.0% to 58.1%), and 3.3% to 9.4% had used clonidine before. In [Tourette's Syndrome Study Group](#)

(2002), between 45% and 63% had previously used stimulants, and between 27% and 56% had used clonidine.

There are several rating scales used to assess treatment response in ADHD and the trials used various scales to measure ADHD symptoms, including Conners behaviour checklist and Conners abbreviated symptom questionnaires. Some of these rating scales are scored by teachers and others by parents. The trials report whether or not treatments had a statistically significant effect on these rating scales. However, it is difficult to establish whether statistically significant effects on these scales are also clinically significant.

The study populations varied significantly. [Palumbo et al. \(2008\)](#) recruited children with mixed ADHD subtypes (excluding tic disorders); [Hazell et al. \(2003\)](#) recruited only those with ADHD and oppositional defiant disorder or conduct disorder; and [Tourette's Syndrome Study Group \(2002\)](#) recruited only those with ADHD and tic disorders. [Palumbo et al. \(2008\)](#) noted that baseline ADHD symptom profiles differed between their study population and those with tic disorder recruited by [Tourette's Syndrome Study Group \(2002\)](#) and suggested that this may affect treatment response.

Children and young people with cardiovascular disorders were excluded from studies by [Hazell et al. \(2003\)](#), [Palumbo et al. \(2008\)](#) and [Tourette's Syndrome Study Group \(2002\)](#). Therefore, efficacy and safety findings cannot be applied to this subgroup, who may be more at risk of serious adverse events than those included in the RCTs.

Parents accurately guessed treatment allocation in [Hazell et al. \(2003\)](#), possibly because of the sedation effect of clonidine in the first few weeks of treatment, so this trial was effectively unblinded. This may have biased the results in favour of treatment especially as the primary outcome was parent-reported differences in ADHD symptoms.

Evidence submitted to the US Food and Drug Administration to support the marketing authorisation of clonidine extended-release tablets ([Kapvay](#)) in the USA has not been reviewed in this evidence summary. This is because expert advice indicated that unlicensed use of extended-release clonidine was very limited in UK clinical practice, and the larger and more relevant issue was off-label use of the standard-release formulations available in the UK.

Summary for patients

A [summary written for patients](#) is available on the NICE website.

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Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [interim process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

1 NHS Evidence

2 NICE

3 Euroscan

4 Broad internet search: Google e.g.: drug name/condition AND (~guideline OR ~algorithm)
filetype:pdf

5 Scirus

MEDLINE (via Ovid)

1 exp review/ (1738622)

2 (scisearch or psychinfo or psycinfo or medlars or embase or psychlit or psyclit or cinahl or
pubmed or medline).ti,ab,sh. (69394)

3 ((hand adj2 search\$) or (manual\$ adj2 search\$)).ti,ab,sh. (6064)

4 ((electronic or bibliographic or computeri?ed or online) adj4 database\$).ti,ab. (13489)

5 (pooling or pooled or mantel haenszel).ti,ab,sh. (45101)

6 (peto or dersimonian or der simonian or fixed effect).ti,ab,sh. (2590)

7 or/2-6 (119360)

8 1 and 7 (52960)

9 Meta Analysis/ (36589)

10 (meta-analys\$ or meta analys\$ or metaanalys\$).ti,ab,sh. (64906)

11 ((systematic\$ or quantitativ\$ or methodologic\$) adj5 (review\$ or overview\$ or synthesis\$)).ti,ab,sh. (52009)

12 (integrative research review\$ or research integration).ti,ab,sh. (81)

13 or/9-12 (101062)

14 8 or 13 (128565)

15 clinical trials, phase iv/ or clinical trials, phase iii/ or randomized controlled trials/ or multicenter studies/ (233755)

16 (random\$ or placebo\$ or ((singl\$ or double\$ or triple\$ or treble\$) and (blind\$ or mask\$))).ti,ab,sh. (862804)

17 15 or 16 (957199)

18 (animal\$ not human\$).sh. (3660265)

19 17 not 18 (853758)

20 19 and 14 (47507)

21 exp "Attention Deficit and Disruptive Behavior Disorders"/ (20051)

22 (hyperactiv* or adhd or "attention deficit").ab,ti. (36749)

23 21 or 22 (42937)

24 Clonidine/ (12346)

25 (clonidine or clon-ir or clon-xr or catapres).tw. (13055)

26 24 or 25 (16313)

27 23 and 26 (449)

28 14 and 27 (15)

29 19 and 27 (69)

30 28 or 29 (78)

31 limit 30 to english language (75)

32 (cost\$ or economic\$).tw. (418369)

33 27 and 32 (7)

Embase (via Ovid)

As above except additional limit:

33 limit 31 to exclude medline journals (55)

Cochrane Central Register of Controlled Trials (CENTRAL)

clonidine or catapres:ti,ab,kw (Word variations have been searched)

MeSH descriptor: [Clonidine] explode all trees

#1 or #2

adhd or hyperactiv* or "attention deficit"

MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] explode all trees

#4 or #5

#3 and #6

CRD HTA, DARE and EED database

(clonidine or catapres) AND (adhd OR hyperactiv* OR "attention deficit")

Grey literature and ongoing trials

1 [FDA](#)

2 [EMA](#)

3 [MHRA](#)

4 [Scottish Medicines Consortium](#)

5 [All Wales Medicine Strategy Group](#)

6 [metaRegister of Controlled Trials \(mRCT\)](#)

7 [ClinicalTrials.gov](#)

Manufacturers' websites

[Boehringer-Ingelheim](#)

Evidence selection

Expert advice indicated that off-label clonidine would only usually be prescribed for children and young people with ADHD as an add-on therapy to stimulants, and mainly in children and young people whose ADHD is unresponsive to, or who are unsuitable for, first-line licensed drug treatment. Experts also indicated that unlicensed use of the extended-release clonidine ([Kapvay](#); approved in the USA but not in the UK) is not currently common in the UK, although this may become more of an issue in the future.

Consequently, our evidence selection focused on identifying randomised controlled trials (RCTs) that used clonidine as add-on therapy (with stimulant medication) to treat ADHD symptoms in children and young people who had already been offered first-line treatments. No restrictions on ADHD subtype were used during the literature search. However, in the study selection, the use of

clonidine in ADHD comorbid with Tourette's syndrome and other chronic tic disorders emerged as an important research area – particularly in relation to the effect of drug treatment on tic symptoms – so key studies were also included as an ADHD comorbid subgroup of potential interest.

RCTs with total study populations of less than 25 children and young people were excluded in study selection ([Connor et al. 2000](#) and [Hunt et al. 1986](#)) because of the presence of larger studies providing higher-quality evidence.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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