Attention deficit hyperactivity disorder in children and young people: guanfacine prolonged-release

Evidence summary

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Key points from the evidence

> The content of this evidence summary was up-to-date in March 2016. See summaries of product characteristics (SPCs), British national formulary (BNF), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Summary

Guanfacine prolonged-release (Intuniv) is a non-stimulant treatment for children and young people with attention deficit hyperactivity disorder (ADHD). In 3 short-term, randomised controlled trials (RCTs) it was more effective than placebo at improving ADHD symptoms, although a beneficial effect on social functioning was not consistently shown. The most frequently reported adverse reactions for guanfacine prolonged-release were somnolence, headache, fatigue, upper abdominal pain and sedation. Serious adverse reactions include hypotension, weight increase, bradycardia and syncope. No studies directly compared the efficacy and safety of guanfacine prolonged-release with other active treatments for ADHD.

Regulatory status: Guanfacine prolonged-release (Intuniv) received a European marketing authorisation for use in ADHD in September 2015. It was launched in the UK in February 2016. Guanfacine prolonged-release is licensed for the treatment of ADHD in children and young people

aged 6–17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. It is not licensed for use in combination with stimulants or for adults with ADHD.

Effectiveness	Safety
• In 1 short-term RCT, dose-optimised guanfacine prolonged-release was more effective than placebo at improving ADHD symptoms in children and young people aged 6–17 years (about half of whom had previously been treated with stimulant medication; p<0.001, effect size=0.76; n=338). • In 2 other short-term RCTs, dose-optimised guanfacine prolonged-release was more effective than placebo at improving ADHD symptoms in young people aged 13–17 years (p<0.001, effect size=0.52; n=314) and in children aged 6–12 years (p<0.001; n=333).	• Guanfacine can cause syncope, hypotension, bradycardia, somnolence, sedation weight gain and QT-interval prolongation. Dose titration and monitoring is required at the start of treatment (Summary of Product Characteristics [SPC] for guanfacine prolonged-release). • Blood pressure and pulse may increase following discontinuation of guanfacine. Monitoring and tapering of the dose during withdrawal is recommended (SPC for guanfacine prolonged-release). • The most frequently reported adverse reactions include somnolence, headache, fatigue, upper abdominal pain upper, and sedation (SPC for guanfacine prolonged-release). • Rates of treatment-emergent adverse events were higher in children and young people treated with guanfacine compared with atomoxetine or placebo (European Public Assessment Report [EPAR] for Intuniv [guanfacine prolonged-release]).

Patient factors	Resource implications
• There are pre-treatment screening and monitoring requirements for somnolence and sedation, cardiovascular status, heart rate, blood pressure, height, weight and body mass index (SPC for guanfacine prolonged-release). • Somnolence and sedation can occur mainly at the start of treatment, typically lasting for 2–3 weeks and longer in some cases (SPC for guanfacine prolonged-release). • Undesirable side effects are common and limit tolerability (EPAR for Intuniv [guanfacine prolonged-release]).	• Guanfacine prolonged-release tablets (Intuniv) cost £56.00–£141.68 for 28 days treatment at a dose of 1–7 mg daily (excluding VAT; MIMS, February 2016). • Atomoxetine capsules (Strattera) cost £62.46–£83.28 for 28 days treatment at a dose of 10–100 mg daily (excluding VAT; Drug Tariff February 2016). • Atomoxetine 4 mg/ml oral solution (Strattera) costs £23.33–£233.33 for 28 days treatment at a dose of 10–100 mg daily (excluding VAT; Drug Tariff, February 2016).

Introduction and current guidance

Attention deficit hyperactivity disorder (ADHD) is a heterogeneous behavioural syndrome characterised by the core symptoms of hyperactivity, impulsivity and inattention. The NICE guideline on ADHD (currently being updated, publication expected January 2018) covers diagnosing and managing ADHD in children, young people and adults. Where drug treatment is considered appropriate, the guideline recommends methylphenidate, atomoxetine and dexamfetamine within their licensed indications, as options for the management of ADHD in children and young people. Choice of drug should be guided by comorbidities, adverse effects, specific issues that may affect compliance, the potential for drug diversion or misuse, and the preferences of the child or young person or their parent or carer.

Full text of introduction and current guidance.

Product overview

Guanfacine is a selective alpha2–adrenergic receptor agonist. It is a non-stimulant.

Guanfacine prolonged-release (Intuniv) is licensed for the treatment of ADHD in children and young people aged 6–17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective (Intuniv [guanfacine prolonged-release] SPC).

The recommended maintenance dose range for guanfacine prolonged-release is 0.05–0.12 mg/kg/day, based on the person's response and tolerability. The recommended starting dose is 1 mg once a day. The dose may be adjusted in increments of not more than 1 mg per week. The maximum dose for children aged 6–12 years is 4 mg daily; for young people aged 13–17 years the maximum dose is dependent on weight, with a maximum dose of 7 mg daily for young people weighing 58.5 kg and above. The SPC provides recommended dose titration tables, based on age and weight.

Guanfacine prolonged-release is not licensed in adults with ADHD.

Guanfacine prolonged-release is available in 28 tablet packs, costing £56.00 for 28×1 mg; £58.52 for 28×2 mg; £65.52 for 28×3 mg and £76.16 for 28×4 mg (MIMS, February 2016, prices exclude VAT).

Full text of product overview.

Evidence review

This evidence summary is based on 1 randomised controlled trial (RCT) that involved children and young people aged 6–17 years who received dose-optimised guanfacine prolonged-release (Hervas et al. 2014). Other RCTs discussed include a study involving young people aged 13–17 years who received dose-optimised guanfacine; an RCT involving children aged 6–12 years that compared dose-optimised guanfacine given in the morning and evening; and an RCT involving children aged 6–12 years with ADHD and oppositional symptoms who received dose-optimised guanfacine. Additional safety and efficacy data from 2 open-label, long-term extension studies are discussed, along with results of a phase 2 RCT that assessed the effect of guanfacine on psychomotor functioning and alertness.

- In a short-term RCT involving 338 children and young people with ADHD (about half of whom had previously been treated with stimulant medication), dose-optimised guanfacine prolonged-release was statistically significantly more effective than placebo at improving ADHD symptoms, measured using the validated ADHD Rating Scale version IV (ADHD-RS-IV) score at 10 or 13 weeks (Hervas et al. 2014). The placebo-adjusted difference in LS mean change from baseline in ADHD-RS-IV score for guanfacine was −8.9 points (95% confidence interval [CI] −11.9 to −5.8, p<0.001, effect size 0.76). This study included an atomoxetine arm,

but was not powered to test superiority of guanfacine over atomoxetine. The placebo-adjusted difference in LS mean change from baseline in ADHD-RS-IV score for atomoxetine was −3.8 points (95% CI −6.8 to −0.7, p=0.017, effect size 0.32).

- A 13-week RCT compared guanfacine prolonged-release with placebo in 314 young people aged 13–17 years with ADHD (Wilens et al. 2015). At study end there was a statistically significant improvement in ADHD-RS-IV score for guanfacine compared with placebo. In the guanfacine group the LS mean change from baseline was −24.6 points compared with −18.5 points for placebo, p<0.001, effect size 0.52.

- An 8-week, placebo-controlled RCT compared morning and evening administration of dose-optimised guanfacine prolonged-release in 333 children aged 6–12 years with ADHD (Newcorn et al. 2013). Both morning and evening dosing showed a statistically significant improvement over placebo in mean ADHD-RS-IV score from baseline, with no difference between the 2 times of administration (−19.8 points with guanfacine morning dosing, −20.1 with guanfacine evening dosing and −11.0 with placebo; p<0.001 for both guanfacine groups compared with placebo).

- The efficacy of guanfacine prolonged-release in children with ADHD and oppositional symptoms was assessed in a 9-week, flexible-dose, double-blind, RCT (Connor et al. 2010, n=217). A statistically significantly greater reduction in the oppositional subscale of the Conners' Parent Rating Scale-Revised: Long Form (CPRS-R:L) score was seen for guanfacine compared with placebo (LS mean change from baseline: −10.9 points with guanfacine and −6.8 points with placebo, p<0.001, effect size 0.59).

- Two open-label extension studies have reported on the long-term effectiveness of guanfacine prolonged-release for up to 2 years (Sallee et al. 2009b and Biederman et al. 2008b). In Sallee et al. 2009b, participants receiving guanfacine monotherapy had a mean ADHD-RS-IV score of 40.6 points at baseline, reducing to 19.4 points at study end (mean score reduction 21.2 points, p<0.001). In Biederman et al. 2008b the ADHD-RS-IV score reduced by 18.1 points from baseline to study end (p<0.001). Discontinuation rates were high, with approximately 80% of participants across the 2 studies leaving before 24 months.

- The EPAR for Intuniv (guanfacine prolonged-release) reports that there is uncertainty about the effect of guanfacine on social functioning, with only 1 study (Hervas et al. 2014) showing statistically significant results.

- The EPAR states that rates of treatment-emergent adverse events were higher in children and young people treated with guanfacine compared with atomoxetine or placebo. Severe adverse events were reported in 8.8%, 1.8% and 1.7% of those taking guanfacine, atomoxetine and

placebo respectively. Adverse events considered to be related to the study drug occurred in 73.2% of people taking guanfacine (1765/2411), 55.4% of those taking atomoxetine (62/112) and 36.7% of those taking placebo (357/973). Discontinuation rates due to adverse events were higher in the guanfacine group (10.8%; 261/2411) compared with the atomoxetine group (4.5%; 5/112) or the placebo group (1.3%; 13/973).

- The SPC for Intuniv (guanfacine prolonged-release) states that in clinical studies the most frequently reported adverse reactions include somnolence (40.6%), headache (27.4%), fatigue (18.1%), upper abdominal pain (12.0%) and sedation (10.2%). Serious adverse reactions include hypotension (3.2%), weight increase (2.9%), bradycardia (1.5%) and syncope (0.7%). The SPC notes that somnolence and sedation occur predominantly at the start of treatment and may typically last for 2–3 weeks and longer in some cases.

- The efficacy and safety of guanfacine prolonged-release has not been directly compared to other active treatments for ADHD. All RCTs discussed in this evidence summary were short-term, lasting no more than 13 weeks. The beneficial effect of guanfacine on social functioning has not been consistently shown in clinical trials.

Full text of evidence review.

Context

Guanfacine prolonged-release is licensed specifically for the treatment of ADHD in children and young people aged 6–17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. The only other non-stimulant drug licensed for ADHD in the UK is atomoxetine (a selective noradrenaline reuptake inhibitor). Unlicensed or off-label drug treatment options for ADHD include bupropion, clonidine, modafinil and imipramine.

Full text of context.

Estimated impact for the NHS

The NICE guideline on ADHD recommends that drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions. Where drug treatment is considered appropriate, the guideline recommends methylphenidate, atomoxetine and dexamfetamine, within their licensed indications, as options for the management of ADHD in children and young people.

Guanfacine prolonged-release is licensed for the treatment of ADHD in children and young people aged 6–17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. It must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures (SPC).

The EPAR concluded that treatment with guanfacine prolonged-release resulted in a clinically meaningful improvement in ADHD symptoms, although an effect on social functioning was not consistently shown. However, the safety profile is characterised by undesirable side effects which are common and limit tolerability. These include (orthostatic) hypotension, bradycardia, sedation, fatigue, and headache. There are no studies that directly compare the efficacy and safety of guanfacine prolonged-release with other active treatments for ADHD.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using guanfacine prolonged-release or other treatments for ADHD.

Full text of estimated impact for the NHS.

> **About this evidence summary**
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> 'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

Full evidence summary

Introduction and current guidance

The NICE guideline on attention deficit hyperactivity disorder (ADHD, currently being updated, expected January 2018) describes ADHD as a heterogeneous behavioural syndrome characterised by the core symptoms of hyperactivity, impulsivity and inattention. While these symptoms tend to cluster together, some people are predominantly hyperactive and impulsive, while others are principally inattentive. Symptoms of ADHD can overlap with symptoms of other related disorders, and ADHD cannot be considered a categorical diagnosis. Children with ADHD have an increased risk of psychiatric comorbidities, present in almost two-thirds of paediatric cases; the most common being oppositional defiant disorder (50%), conduct disorder (35%), anxiety disorder (33%), and depression (33%) (Punja et al. 2016).

The NICE guideline on ADHD states that for a diagnosis of ADHD, symptoms of hyperactivity, impulsivity or inattention should:

- meet the diagnostic criteria in DSM-IV or ICD-10 (hyperkinetic disorder), and

- be associated with at least moderate psychological, social, educational or occupational impairment based on interview or direct observation in multiple settings, and

- be pervasive, occurring in 2 or more important settings including social, familial, educational or occupational settings.

It is expected that successful treatment of ADHD will address not only symptomatic improvement but also alleviate impairment in social functioning. Such improvement needs to be demonstrated in clinical trials for ADHD medication (Intuniv [guanfacine prolonged-release] European Public Assessment Report [EPAR]).

The NICE guideline on ADHD recommends group-based parent-training or education programmes as the usual first-line treatment for parents and carers of children and young people of school age with ADHD and moderate impairment. This may also include group psychological treatment (cognitive behavioural therapy [CBT] or social skills training) for the younger child. For older age groups, individual psychological treatment may be more acceptable if group behavioural or psychological approaches have not been effective, or have been refused. Drug treatment should be reserved for those with moderate impairment who have refused non-drug interventions, or those whose symptoms have not responded sufficiently to the first-line interventions.

The NICE guideline recommends drug treatment as the first-line treatment for school-age children and young people with severe ADHD (hyperkinetic disorder) and severe impairment. If the child or young person wishes to refuse medication or the parents or carers reject it, a psychological intervention may be tried but drug treatment has more benefits and is superior to other treatments for this group.

Where drug treatment is considered appropriate, the NICE guideline on ADHD recommends methylphenidate, atomoxetine and dexamfetamine, within their licensed indications, as options for the management of ADHD in children and young people. Choice of drug should be guided by comorbidities, adverse effects, specific issues that may affect compliance, the potential for drug diversion or misuse, and the preferences of the child or young person or their parent or carer. The guideline recommends that 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 is a choice of more than 1 appropriate drug, the product with the lowest cost (taking into account the cost per dose and number of daily doses) should be prescribed. The guideline recommends that dexamfetamine should be considered in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine. For 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 the use of unlicensed or off-label medicines for ADHD (such as bupropion, clonidine, modafinil and imipramine) or combination treatments (including psychological treatments for the parent or carer and the child or young person). The use of unlicensed or off-label medicines for ADHD should only be considered in the context of tertiary services.

Product overview

Drug action

Guanfacine is a selective alpha2–adrenergic receptor agonist. It is a non-stimulant. The mechanism of action of guanfacine in ADHD is not fully established. It has been hypothesised that guanfacine modulates signalling in the prefrontal cortex, thereby restoring deficits in attention and impulse control (Intuniv [guanfacine prolonged-release] summary of product characteristics [SPC] and Intuniv [guanfacine prolonged-release] European Public Assessment Report [EPAR]).

Licensed therapeutic indication

Guanfacine prolonged-release (Intuniv) is licensed for the treatment of ADHD in children and young people aged 6–17 years for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. It must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures. Treatment must be initiated under the supervision of an appropriate specialist (Intuniv [guanfacine prolonged-release] SPC).

Guanfacine prolonged-release is not licensed in adults with ADHD.

Guanfacine prolonged-release received a European marketing authorisation in September 2015, and was launched in the UK in February 2016.

Course and cost

The recommended starting dose of guanfacine prolonged-release is 1 mg once a day. The dose may be adjusted in increments of not more than 1 mg per week. Dose should be individualised according to the patient's response and tolerability. The recommended maintenance dose range for guanfacine prolonged-release is 0.05–0.12 mg/kg/day, based on the person's response and tolerability (Intuniv [guanfacine prolonged-release] SPC).

The SPC provides recommended dose titration tables, based on age and weight. The maximum dose for children aged 6–12 years is 4 mg daily; for young people aged 13–17 years the maximum dose is dependent on weight, with a maximum dose of 7 mg daily for young people weighing 58.5 kg and above.

Guanfacine prolonged-release is available in 28 tablet packs, costing £56.00 for 28×1 mg; £58.52 for 28×2 mg; £65.52 for 28×3 mg and £76.16 for 28×4 mg. Therefore, 28 days' supply at a dose of 4 mg daily costs £76.16 and a dose of 7 mg daily costs £141.68 (all prices from MIMS, February 2016, prices exclude VAT).

Evidence review

This evidence summary is based on 1 randomised controlled trial (RCT) that involved children and young people aged 6–17 years who received dose-optimised guanfacine prolonged-release (Hervas et al. 2014). Other RCTs are discussed briefly. These include an RCT involving young people aged 13–17 years who received dose-optimised guanfacine; an RCT involving children aged 6–12 years that compared dose-optimised guanfacine given in the morning and evening; and an RCT involving children aged 6–12 years with ADHD and oppositional symptoms who received dose-optimised guanfacine. Additional safety and efficacy data from 2 open-label, long-term extension studies are discussed, along with results of a phase 2 RCT that assessed the effect of guanfacine on psychomotor functioning and alertness.

Assessment tools used in clinical trials

The primary end point of most studies discussed in this evidence summary was improvement in ADHD symptoms, measured using the validated ADHD Rating Scale version IV (ADHD-RS-IV). This is an 18-item questionnaire examining inattention (9 items) and hyperactivity–impulsivity (9 items),

with each item scored from 0 (no symptoms) to 3 (severe symptoms). The total score ranges from 0 to 54, with higher scores indicating more severe symptoms (Sallee et al. 2009a).

An improvement in social functioning is an important treatment goal in ADHD, and this was measured in some studies using the Weiss Functional Impairment Rating Scale Parent Report (WFIRS-P). The WFIRS-P is a tool completed by the parent who scores distinct domains (school [learning and behaviour] or work, family, social, leisure, self-concept, and risky activities) on a 4-point Likert scale, with higher scores indicating greater functional impairment (total of 50 questions; maximum score of 150 points).

Hervas et al. 2014

- Design: randomised, double-blind, multicentre, dose-optimised, placebo- and active-controlled trial conducted in the USA, Canada and Europe (including centres in the UK).

- Population: 338 children and young people aged 6–17 years (mean age 10.8 years, 71.8% aged 6–12 years) with ADHD (85.2% with combined subtype of ADHD) were randomised. Participants were required to have a diagnosis of ADHD of at least moderate severity, with an ADHD-RS-IV score of 32 or more and a Clinical Global Impression-Severity (CGI-S) score of 4 or more. The mean ADHD-RS-IV score at baseline was 43.3, the mean time since diagnosis was 2.2 years and approximately half the participants had previously been treated with stimulant medication. Children and young people with a current comorbid psychiatric condition (except oppositional defiant disorder) were excluded from the study, along with those with a known history of cardiac problems, hypertension, orthostatic hypotension and syncope.

- Intervention and comparison: participants were randomised 1:1:1 to guanfacine prolonged-release, atomoxetine or placebo; allocation was concealed. Atomoxetine was included as an internal reference against placebo; the study was not designed to provide a head-to-head comparison between guanfacine and atomoxetine. Both active treatments were dose optimised. The guanfacine was dose-optimised between 0.05–0.12 mg/kg/day, equating to a daily dose of 1–4 mg for participants aged 6–12 years and 1–7 mg for those aged 13–17 years (dependant on weight). Guanfacine was started at a dose of 1 mg daily, and increased in 1 mg increments no quicker than once weekly. The atomoxetine dose was titrated based on weight; participants weighing less than 70 kg were initiated at 0.5 mg/kg/day, increasing to a target of 1.2 mg/kg/day and a maximum of 1.4 mg/kg/day if tolerated. Participants weighing 70 kg or more were started at 40 mg/day atomoxetine, increasing to 80 mg/day after 1 week and finally up to the maximum dose of 100 mg/day if required. Participants were considered to be at optimal dose if they achieved a 30% or more reduction in ADHD-RS-IV score from baseline and a CGI-Improvement (CGI-I) score of 1 or 2. For both

active treatments the length of the titration period was determined by age: children aged 6–12 years were titrated over 4 weeks and adolescents aged 13–17 years were titrated over 7 weeks. Following dose optimisation the mean daily dose of guanfacine prolonged-release was 3.6 mg (standard deviation [SD] 1.3 mg), and for atomoxetine 42.1 mg (SD 20.1 mg). The mean weight-adjusted optimal dose for guanfacine was 0.09 (SD 0.03) mg/kg/day, and 1.03 (SD 0.21) mg/kg/day for atomoxetine. On completion of the double-blind phase, doses were tapered downward over a 2-week period, with a follow-up safety visit 1 week after discontinuation.

- Outcome: the primary efficacy end point was change from baseline in ADHD-RS-IV score at visit 15 (end of double-blind phase; week 10 for participants aged 6–12 years and week 13 for participants aged 13–17 years). Key secondary end points were change from baseline to visit 15 in CGI-I rating scale, and the learning and school domain and family domain of WFIRS-P. All outcome measures used last observation carried forward (LOCF) methodology.

Table 1 Summary of Hervas et al. 2014

	Guanfacine prolonged-release (1–7 mg daily, dose optimised)	Atomoxetine (10–100 mg daily, dose optimised)	Placebo	Analysis
Randomised	n=115	n=112	n=111	
Efficacy[a]	n=114	n=112	n=111	
Primary outcome: change in ADHD-RS-IV score from baseline to visit 15 (SD)[b]	−23.9 (12.4) from baseline of 43.1 (5.4)	−18.6 (11.91) from baseline of 43.7 (5.86)	−15.0 (13.07) from baseline of 43.2 (5.60)	Guanfacine: difference in LS means compared with placebo: −8.9 (95% CI −11.9 to −5.8, p<0.001), effect size=0.76 Atomoxetine: difference in LS means compared with placebo: −3.8 (95% CI −6.8 to −0.7, p=0.017), effect size=0.32
Selected secondary outcomes				

Participants showing an improvement in CGI-I score at visit 15[c]	67.9% (76/114)	56.3% (63/112)	44.1% (49/111)	Guanfacine: difference compared with placebo: 23.7% (95% CI 11.1% to 36.4%, p<0.001) Atomoxetine: difference compared with placebo: 12.1% (95% CI −0.9% to 25.1%, p=0.024)
Change from baseline to week 15 in WFIRS-P learning and school domain[d]	−0.64[e]	−0.58[e]	−0.42[e]	Guanfacine: LS mean difference compared with placebo, −0.22 (95% CI −0.36 to −0.08, p=0.003) effect size=0.42 Atomoxetine: LS mean difference compared with placebo, −0.16 (95%CI −0.31 to −0.02, p=0.026) effect size=0.32
Change from baseline to week 15 in WFIRS-P family domain[d]	−0.62[e]	−0.50[e]	−0.41[e]	Guanfacine: LS mean difference compared with placebo, −0.21 (95% CI −0.36 to −0.06, p=0.006) effect size=0.38 Atomoxetine: LS mean difference compared with placebo, −0.09 (95%CI −0.24 to 0.06, p=0.242) effect size=0.16

Safety[a]	n=114	n=112	n=111	
Participants reporting treatment emergent adverse events	77.2% (88/114)	67.9% (76/112)	65.8% (73/111)	No statistical analysis reported
Participants reporting severe treatment emergent adverse events	7.0% (8/114)	1.8% (2/112)	2.7% (3/111)	No statistical analysis reported
Participants with treatment emergent adverse events leading to withdrawal	7.9% (9/114)	4.5% (5/112)	0.9% (1/111)	No statistical analysis reported

Abbreviations: CI, confidence interval; LS, least square; p, p value.

[a] Full analysis set: all randomised participants who received at least 1 dose of study drug.

[b] ADHD-RS-IV: measure of symptom severity in ADHD. An 18-item questionnaire, with each item scored from 0 (no symptoms) to 3 (severe symptoms). The total score ranges from 0 to 54, with higher scores indicating more severe symptoms.

[c] CGI-I: Clinical Global Impression-Improvement rating scale. An assessment of improvement, where the response to study treatment is scored from 1 (very much improved) to 7 (very much worse).

[d] WFIRS-P: Weiss Functional Impairment Rating Scale Parent Report. A tool completed by the parent who scores distinct domains (school [learning and behaviour] or work, family, social, leisure, self-concept, and risky activities) on a 4-point scale. Higher scores indicate greater functional impairment.

[e] Results taken from European Public Assessment Report for guanfacine.

Clinical effectiveness

Guanfacine prolonged-release has been assessed in 3 RCTs (Hervas et al. 2014, Wilens et al. 2015 and Newcorn et al. 2013) that used a flexible-dose treatment regimen similar to the recommended dose titration tables included in the Intuniv [guanfacine prolonged-release] SPC.

In Hervas et al. 2014, a short-term RCT involving 338 children and young people (aged 6–17 years) with ADHD, dose-optimised guanfacine prolonged-release was statistically significantly more effective than placebo at improving ADHD-RS-IV score at 10 or 13 weeks. The least squares (LS) mean change from baseline in ADHD-RS-IV score for guanfacine was −23.9 points compared with −15.0 points for placebo. The placebo-adjusted difference in LS mean change from baseline in ADHD-RS-IV score for guanfacine was −8.9 points (95% confidence interval [CI] −11.9 to −5.8, p<0.001, effect size 0.76). The minimal clinically important difference on this rating scale is debated. However this is larger than the minimal clinically important difference of −6.6 points suggested by Zhang et al. 2005. The study by Hervas et al. 2014 also included an atomoxetine arm. It was not powered to test superiority of guanfacine over atomoxetine, but the change in ADHD-RS-IV score was numerically higher for guanfacine than for atomoxetine. The placebo-adjusted difference in LS mean change from baseline in ADHD-RS-IV score for atomoxetine was −3.8 points (95% CI −6.8 to −0.70, p=0.017, effect size 0.32).

The proportion of participants in Hervas et al. 2014 showing an improvement in CGI-I (1, very much improved, or 2, much improved) at study end were 67.9% for guanfacine, 56.3% for atomoxetine and 44.1% for placebo: a statistically significant difference compared with placebo for both active treatments (see table 1 for details).

Statistically significant improvements in placebo-adjusted difference in LS mean change from baseline in WFIRS-P learning and school domain were seen for guanfacine (−0.22, 95%CI −0.36 to −0.08, p=0.003, effect size 0.42) and for atomoxetine (−0.16, 95% CI −0.31 to −0.02, p=0.026, effect size 0.32). Statistically significant improvements in WFIRS-P family domain were also seen for guanfacine (−0.21, 95% CI −0.36 to −0.06, p=0.006, effect size 0.38), but not for atomoxetine (−0.09, 95% CI −0.24 to 0.06, p=0.242, effect size 0.16).

The efficacy of guanfacine in young people aged 13–17 years with ADHD has been examined in a 13-week, multicentre, dose-optimised, double-blind, placebo-controlled RCT by Wilens et al. 2015. A total of 314 young people were randomised to guanfacine prolonged-release (n=157) or placebo (n=157). Similar inclusion criteria as Hervas et al. 2014 were used; a diagnosis of ADHD, with an ADHD-RS-IV score of 32 or more and a CGI-S score of 4 or more. The mean age was 14.5 years, the majority of the participants were male (64.7%) and had the combined ADHD subtype (67.9%). Previous treatment with stimulants was reported in 70.1% of people receiving guanfacine and 77.4% receiving placebo. The mean time since diagnosis of ADHD was 5.1 years. Guanfacine was started at a dose of 1 mg daily and titrated to optimal dose over 7 weeks, up to the maximum dose based on the participant's weight in the absence of significant safety or tolerability issues. As in Hervas et al. 2014, participants were considered to be at optimal dose if they achieved a 30% or more reduction in ADHD-IV-RS score from baseline and a CGI-I score of 1 or 2. For participants

who achieved these improvements but could potentially achieve additional symptom reduction, the dose could be increased further. The mean optimised guanfacine dose was 4.3 mg daily. The primary efficacy end point was change from baseline in the ADHD-RS-IV score at week 13. Key secondary end points included CGI-S score and the WFIRS-P learning and school domain and family domain.

At week 13 there was a statistically significant improvement in ADHD-RS-IV score for guanfacine compared with placebo. In the guanfacine group the LS mean change from baseline was −24.6 points compared with −18.5 points for placebo, p<0.001, effect size 0.52 (baseline score not reported). Statistically significantly more people treated with guanfacine achieved a CGI-S score of 2 or less compared with placebo (50.6% and 36.1% respectively, p=0.01). There was no statistically significant difference between groups for any WFIRS-P domain score.

In an 8-week, double-blind, placebo-controlled RCT, Newcorn et al. 2013 compared morning and evening administration of dose-optimised guanfacine in 333 children aged 6–12 years with ADHD. Mean age was 9.1 years and most participants were male (70.6%) with the combined ADHD subtype (96.1%). Participants were randomised to guanfacine prolonged-release 1–4 mg in the morning (n=107), evening (n=114) or placebo (n=112). The study consisted of a 5-week dose optimisation period followed by a 3-week maintenance period. A participant was considered to be at the optimal dose when they had a reduction of 30% or more in ADHD-RS-IV score from baseline with an acceptable level of side effects. The mean optimal dose of guanfacine was 2.9 mg daily. The mean ADHD-RS-IV score at baseline was approximately 42 points.

The primary efficacy end point was mean change in ADHD-RS-IV score from baseline to study end. Both morning and evening dosing showed a statistically significant improvement over placebo, with no difference between the 2 times of administration (−19.8 points with guanfacine morning dosing, −20.1 with guanfacine evening dosing and −11.0 with placebo; p<0.001 for both guanfacine groups compared with placebo).

The efficacy of guanfacine in 217 children aged 6–12 years with ADHD and oppositional symptoms was assessed in a 9-week, dose-optimised, double-blind, placebo-controlled RCT by Connor et al. 2010. Participants were required to have a diagnosis of ADHD, with an ADHD-RS-IV score of 24 or more and a score of 14 or more for males, 12 or more for females, on the oppositional subscale of the Conners' Parent Rating Scale-Revised: Long Form (CPRS-R:L). The CPRS-R:L oppositional subscale contains 10 questions in which parents are asked to rate the presence of symptoms such as ''loses temper'', ''spiteful'' or ''fights'' between 0 and 3 (maximum score 30), with higher scores representing more severe or frequent symptoms. Participants were randomised to dose-optimised

guanfacine prolonged-release 1–4 mg daily (n=138) or placebo (n=79) for a 5-week titration phase, a 3-week maintenance phase and a 1-week tapering period.

There was a statistically significantly greater reduction in the primary end point, a change in the oppositional subscale of the CPRS-R:L score from baseline to end point, with guanfacine compared with placebo (LS mean change from baseline: −10.9 points with guanfacine and −6.8 points with placebo, p<0.001, effect size 0.59). Statistically significant improvements in ADHD symptoms, a secondary end point, were also seen (LS mean change from baseline in ADHD-RS-IV score: −23.8 points with guanfacine compared with −11.5 points with placebo, p<0.001, effect size 0.92).

Similar results to those from the flexible-dose studies were observed in 2 fixed-dose, 8 or 9-week, placebo-controlled RCTs in children and young people aged 6–17 years with ADHD (Biederman et al. 2008a [n=345] and Sallee et al. 2009a [n=324]). The SPC for guanfacine prolonged-release recommends that the dose should be individualised according to the person's response and tolerability, so fixed-dose studies may not reflect how the drug is used in clinical practice and these studies are not discussed further.

Two open-label extension studies have reported on the long-term effectiveness of guanfacine for up to 2 years (Sallee et al. 2009b and Biederman et al. 2008b). Sallee et al. 2009b (n=262) was an extension study to the fixed-dose study by Sallee et al. 2009a and a phase 2, open-label study that involved the co-administration of guanfacine prolonged-release and psychostimulants (Spencer et al. 2009). Biederman et al. 2008b (n=240) was an extension study to the fixed-dose study by Biederman et al. 2008a. Neither long-term study included a placebo group. In both extension studies participants were titrated to their optimal dosage up to a maximum dose of 4 mg daily and remained on this dose for 24 months.

The main efficacy outcome in both extension studies was change in ADHD-RS-IV score from baseline (of the initial short-term study) to the end of the 24 month extension period. In Sallee et al. 2009b, participants receiving guanfacine monotherapy had a mean ADHD-RS-IV score of 40.6 points at baseline, reducing to 19.4 points at study end; mean score reduction 21.2 points, p<0.001. In Biederman et al. 2008b the ADHD-RS-IV score reduced by 18.1 points from baseline to study end (p<0.001, actual scores at both time points not reported).

Discontinuation rates in both studies were high, with 77.1% (202/262) of participants in Sallee et al. 2009b and 82.5% (198/240) in Biederman et al. 2008b discontinuing before 24 months. The most common reason for discontinuation in both studies was withdrawal of consent. The EPAR states that while the high drop-out rate raised some uncertainties, the results of these 2 extension studies suggest that efficacy is maintained in the long-term in people who continue treatment.

Safety and tolerability

In Hervas et al. 2014, 77.2% (88/114) of people receiving guanfacine reported treatment emergent adverse events, compared with 67.9% (76/112) for atomoxetine and 65.8% (73/111) for placebo. The majority of treatment emergent adverse events were of mild or moderate intensity. The most common adverse events reported with guanfacine were somnolence, headache and fatigue; with atomoxetine they were decrease in appetite, nausea and fatigue. Adverse events led to study discontinuation in 7.9% (9/114) of the guanfacine group, 4.5% (5/112) of the atomoxetine group and 0.9% (1/111) of the placebo group.

The European Public Assessment Report (EPAR) for Intuniv (guanfacine prolonged-release) reports on safety data for 2411 children and young people with ADHD (aged 6–17 years) who received guanfacine prolonged-release. The majority of people exposed were aged 6–12 years (71%, 1718/2411), with a mean duration of exposure of 142 days and a median exposure time of 70 days.

The EPAR states that rates of treatment-emergent adverse events were higher in people treated with guanfacine compared with atomoxetine or placebo. Severe adverse events were reported in 8.8%, 1.8% and 1.7% of those taking guanfacine, atomoxetine and placebo respectively. Adverse events considered to be related to the study drug occurred in 73.2% of people taking guanfacine (1765/2411), 55.4% of those taking atomoxetine (62/112) and 36.7% of those taking placebo (357/973). Discontinuation rates due to adverse events were higher in the guanfacine group (10.8%; 261/2411) compared with the atomoxetine group (4.5%; 5/112) or the placebo group (1.3%; 13/973).

The Summary of Product Characteristics (SPC) for Intuniv (guanfacine prolonged-release) states that in clinical studies the most frequently reported adverse reactions include somnolence (40.6%), headache (27.4%), fatigue (18.1%), upper abdominal pain (12.0%) and sedation (10.2%). Serious adverse reactions include hypotension (3.2%), weight increase (2.9%), bradycardia (1.5%) and syncope (0.7%). The SPC notes that somnolence and sedation occur predominantly at the start of treatment and may typically last for 2–3 weeks and longer in some cases.

Cardiac effects

Cardiovascular effects of guanfacine reported in the EPAR are lowering of blood pressure and pulse, and prolongation of QT-intervals. A dose-dependent decrease in heart rate was seen with guanfacine, together with a dose-dependent prolongation of the QT-interval. In the overall safety population reported in the EPAR, mean heart rate decreased by 9.05 beats per minute (bpm) with guanfacine, compared with a 1.06 bpm decrease with placebo and a 3.26 bpm increase with atomoxetine. A total of 213 participants (10.8%) had a decrease of heart rate to a count of 50 bpm

or less at any time during guanfacine-treatment, compared with 0.8% of participants for placebo and 1.0% for atomoxetine. In the same overall safety population, an on treatment QT-interval of 480 milliseconds or more was seen in 15 participants (0.8%) taking guanfacine, but no participants taking atomoxetine or placebo. After Fridericia-or Bazett-correction there were no intervals of 500 milliseconds or more.

The SPC for guanfacine prolonged-release advises that prior to starting treatment, a person's cardiovascular status (including heart rate, blood pressure and family history of sudden cardiac or unexplained death) should be assessed to identify patients at increased risk of hypotension, bradycardia, and QT-prolongation or risk of arrhythmia. Monitoring of heart rate and blood pressure should continue on a weekly basis during dose titration and stabilisation and at least every 3 months for the first year, taking into consideration clinical judgement. Six monthly monitoring should follow thereafter, with more frequent monitoring following any dose adjustment.

The SPC advises caution when treating people with guanfacine who have a history of hypotension, heart block, bradycardia, or cardiovascular disease, or who have a history of syncope or a condition that may predispose them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Caution is also advised for people taking antihypertensives or other medicines that can reduce blood pressure or heart rate or increase the risk of syncope, and people should be advised to drink plenty of fluid. Blood pressure and pulse may increase following discontinuation of guanfacine; therefore this should be monitored in all children and young people during dose downward titration (decrements of no more than 1 mg every 3 to 7 days) and following discontinuation of guanfacine.

The SPC advises that guanfacine should be prescribed with caution in people with a known history of QT prolongation, risk factors for torsade de pointes (such as heart block, bradycardia or hypokalaemia) or people who are taking medicines known to prolong the QT interval.

Weight gain

Mean body mass index (BMI) increased during the long-term safety studies, from 20.0 kg/m^2 at baseline to 21.8 kg/m^2 at 24 months (EPAR). Since BMI is a predictor for weight-associated health problems in children and young people, the EPAR considers this increase to be a serious concern. The SPC advises that people treated with guanfacine should have their height, weight and BMI monitored before starting treatment, every 3 months for the first year, then every 6 months thereafter, with more frequent monitoring following any dose adjustment.

Cognitive effects

The effect of guanfacine on psychomotor functioning and alertness was assessed in a 45-day, double-blind, placebo-controlled phase 2 RCT in 182 children and young people aged 6–17 years with ADHD (Kollins et al. 2011). Guanfacine prolonged-release was given at a dose of 1–3 mg daily. The optimal dose for most participants was 3 mg daily (58%), and the mean weight adjusted optimal dose was 0.052 mg/kg/day.

The primary end point was reaction time, measured by the Choice Reaction Time (CRT) test from the Cambridge Neuropsychological Test Automated Battery (CANTAB) performed 2, 5, and 8 hours post-dose. Guanfacine did not impair reaction time compared with placebo; least-square (LS) mean difference of 2.5 milliseconds (95% CI −22.9 to 28.0, p=0.84). However, sedative events were reported in 47.8% of patients treated with guanfacine and 28.1% of patients treated with placebo. The EPAR notes that the results of this study reinforce the need to further evaluate the effect of guanfacine on cognitive functioning. The EPAR highlights that the long-term cognitive effects of guanfacine were not evaluated, and impaired learning ability, compromised school performance and delay of cognitive development cannot be excluded in children and young people who are already at risk of delayed cognitive development due to their underlying ADHD disorder.

Evidence strengths and limitations

There are several limitations to the clinical trials discussed in this evidence summary.

None of the studies were designed to directly compare the efficacy and safety of guanfacine prolonged-release with other active treatments for ADHD. Hervas et al. 2014 included atomoxetine as an active control to provide reference data, but the results of this trial cannot be used to determine the most effective treatment because it was not powered to test superiority of guanfacine over atomoxetine. Guanfacine prolonged-release has not been directly compared with stimulants (for example methylphenidate). However, guanfacine prolonged-release is only licensed in the UK for people for whom stimulant treatment is not appropriate, so a comparison with stimulants may not be directly relevant for the licensed indication.

The EPAR reports that in clinical trials, guanfacine prolonged-release showed an inconsistent effect in young people aged 13–17 years. However, this may have been because the doses were too low in the fixed-dose studies, the small sample size in this age group, and a high placebo response in some studies.

The EPAR also reports that there is uncertainty about the effect of guanfacine prolonged-release on social functioning; with only 1 study (Hervas et al. 2014) showing statistically significant results.

While methodological weaknesses in the way this had been assessed in the studies may partially explain these results, the EPAR concluded that an effect on social functioning has not been consistently shown.

All the RCTs included in this evidence summary were short-term, lasting no more than 13 weeks. Two long-term, open-label extension studies (Sallee et al. 2009b and Biederman et al. 2008b) reported 24 month efficacy results, although neither of these studies included a placebo arm and both had very high dropout rates (approximately 80%).

Different dosing schedules were used in the RCTs, with some using a fixed-dose regimen (Biederman et al. 2008a and Sallee et al. 2009) and others allowing for titration up to optimal dose (for example Hervas et al. 2014 and Wilens et al. 2015). These differences in dosage regimens meant that results could not be stratified by dosage in a meta-analysis by Ruggiero et al. 2014. The SPC for guanfacine prolonged-release advises that the dose should be individualised according to response and tolerability, meaning that the fixed-dose trials may not reflect actual clinical practice, and older participants in the trial may not have received high enough doses. The maximum dose of guanfacine used in some trials was 4 mg daily, which is lower than the maximum licensed dose of 7 mg daily (suitable for those aged 13–17 years, weighing 58.5 kg or more).

People with current psychiatric co-morbidity (except for oppositional defiant disorder) were excluded from the clinical trials for guanfacine. Because of this the trial population may not be a true reflection of children and young people with ADHD in the real world (Hervas et al. 2014), since co-morbidities including conduct disorder, anxiety disorder, and depression are common, occurring in approximately one-third of children with ADHD (Punja et al. 2012).

Different inclusion criteria were used in the studies. While all studies required participants to have a diagnosis of ADHD, some required participants to have a baseline ADHD-RS-IV score of 32 or more (Hervas et al. 2014, Wilens et al. 2015), whereas other studies allowed entry for people with an ADHD-RS-IV score of 28 or more (Newcorn et al. 2013) and 24 or more (Connor et al. 2010). There are also differences in efficacy measures used in the clinical trials for guanfacine. A systematic review and meta-analysis by Ruggiero et al. 2014 noted that 11 different tools were used to measure effectiveness, although ADHD-RS-IV and CGI-I were the most frequently used. Ruggiero et al. 2014 also noted that the studies did not report if participants received non-pharmacological interventions, including behavioural or educational therapies, and if the treatment groups were balanced in this respect.

Context

Alternative treatments

Drug treatments for ADHD can be classified into 2 broad categories; stimulants (for example methylphenidate, dexamfetamine and lisdexamfetamine) and non-stimulants (for example atomoxetine, a selective noradrenaline reuptake inhibitor). A NICE evidence summary on lisdexamfetamine dimesylate was published in May 2013.

Guanfacine prolonged-release (Intuniv) is the second non-stimulant treatment for ADHD licensed in the UK. It is licensed specifically for use in children and young people aged 6–17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. Guanfacine prolonged-release is not licensed in the UK for combination treatment with stimulants.

Guanfacine is a selective alpha2–adrenergic receptor agonist. This is the same class of drug as clonidine, which is sometimes used as an off-label treatment for ADHD in the UK (see the NICE evidence summary on clonidine for ADHD, published April 2013).

The NICE guideline on ADHD recommends that drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions. When drug treatment is considered appropriate, methylphenidate, atomoxetine and dexamfetamine are recommended as options, within their licensed indications. For children and young people whose ADHD is unresponsive to these medicines further treatment (such as bupropion, clonidine, modafinil and imipramine, which are unlicensed or off-label medicines for ADHD) should only be considered in the context of tertiary services.

Table 2: Costs of alternative licensed treatments

Drug	Usual dose[a]	28-day cost, excluding VAT
Guanfacine prolonged-release (Intuniv)	1–7 mg daily	£56.00–£141.68[b,c]
Atomoxetine capsules (Strattera)	10–100 mg daily	£62.46–£83.28[c,d]
Atomoxetine 4 mg/1 ml oral solution (Strattera)	10–100 mg daily	£23.33–£233.33[c,d]

^a Taken from the relevant summary of product characteristics. These doses do not represent the full range that can be used and they do not imply therapeutic equivalence.

^b Costs taken from MIMS, February 2016 (excluding VAT).

^c The cost of guanfacine and atomoxetine will depend on the dose used, which would be determined by the person's age, weight, response and tolerability. Both drugs require individual dose adjustments.

^d Costs taken from Drug Tariff, February 2016 (excluding VAT).

Estimated impact for the NHS

Likely place in therapy

The NICE guideline on ADHD (currently being updated, expected January 2018) recommends that drug treatment for children and young people with ADHD should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions. Where drug treatment is considered appropriate, the guideline recommends methylphenidate, atomoxetine and dexamfetamine, within their licensed indications, as options for the management of ADHD in children and young people. The guideline recommends methylphenidate or atomoxetine first, with dexamfetamine a consideration in children and young people whose ADHD is unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine. For children and young people whose ADHD is unresponsive to methylphenidate, atomoxetine and dexamfetamine, further treatment (such as bupropion, clonidine, modafinil and imipramine, which are unlicensed or off-label medicines for ADHD) should only follow after referral to tertiary services.

NICE evidence summaries on lisdexamfetamine dimesylate and clonidine for ADHD have been published.

Guanfacine prolonged-release (Intuniv) is licensed for the treatment of ADHD in children and young people aged 6–17 years old for whom stimulants are not suitable, not tolerated or have been shown to be ineffective. It must be used as a part of a comprehensive ADHD treatment programme, typically including psychological, educational and social measures (Intuniv [guanfacine prolonged-release] SPC).

The EPAR concluded that treatment with guanfacine resulted in a clinically meaningful improvement in ADHD symptoms, although an effect on social functioning was not consistently

shown. Also none of the studies were designed to directly compare the efficacy and safety of guanfacine with other active treatments for ADHD.

A recent systematic review and qualitative analysis by Hollis et al. 2016 concluded that guanfacine was an effective short-term treatment for tics in children and young people with Tourette syndrome; however guanfacine is not licensed for this indication and such use is beyond the scope of this evidence summary.

In common with other alpha2–adrenergic agonists, such as clonidine, the EPAR states that the safety-profile of guanfacine is characterised by undesirable side effects such as (orthostatic) hypotension, bradycardia, sedation, fatigue, and headache. These unwanted effects were shown to be very common and limit tolerability. After discontinuation, in particular after abrupt cessation of treatment, rebound hypertension and tachycardia may occur. The EPAR concluded that the safety of guanfacine was considered to be acceptable. However, the manufacturer is required to conduct a post-authorisation study in order to investigate the long term safety (especially effects on neurocognitive function) of guanfacine.

Local decision makers will need to consider the available evidence on efficacy and safety, as well as cost and individual patient factors, when making decisions about using guanfacine prolonged-release or other treatments for ADHD.

Estimated usage

The manufacturer of guanfacine prolonged-release (Intuniv) estimates that uptake will be as a share of non-stimulants licensed for ADHD, of approximately 10%, 20% and 30% in years 1, 2 and 3 respectively. Prescription Cost Analysis data for 2014 shows that there were approximately 119,000 items for atomoxetine (the only non-stimulant licensed for ADHD at that time) dispensed in primary care in England in 2014. As a percentage of these items, this equates to approximately 12,000 items of guanfacine prolonged-release in year 1, increasing to 36,000 items in year 3 (in primary care only).

Relevance to NICE guidance programmes

Guanfacine prolonged-release (Intuniv) was not considered appropriate for a NICE technology appraisal.

NICE has issued a guideline on attention deficit hyperactivity disorder: diagnosis and management. This is currently being updated, publication expected January 2018. The draft scope for the update includes guanfacine as a specific drug treatment.

NICE has issued technology appraisal guidance on methylphenidate, atomoxetine and dexamfetamine for attention deficit hyperactivity disorder (ADHD) in children and adolescents.

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Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries: new medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

Professor Chris Hollins had no interests to declare.

Noreen Ryan has received advisory board fees from Sandoz and Janssen-Cilag.

Dr Paramala Santosh is a member of the European Network for Hyperkinetic Disorders (Eunethydis), which has obtained educational grants from various pharmaceutical companies, and the European ADHD Guidelines Group (EAGG). Dr Santosh is a Director and shareholder in HealthTracker Limited, a web-based health-monitoring solution.

Professor Ian Wong has received research grants from the Hong Kong Government, the European Union and Janssen-Cilag, and is a member of EAGG.

About this evidence summary

'Evidence summaries: new medicines' provide summaries of key evidence for selected new medicines, or for existing medicines with new indications or formulations, that are considered to be of significance to the NHS. The strengths and weaknesses of the relevant evidence are critically reviewed within this summary to provide useful information for those working on the managed entry of new medicines for the NHS, **but this summary is not NICE guidance.**

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