Safety and efficacy of guanfacine in treating ADHD in children and adolescents: current status of knowledge

A literature study including important factors to consider as a pharmacist in a patient-counselling role

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Abstract

**Introduction** ADHD is a complex chronic neurological disorder that affects circa 5% of school children worldwide and can continue into adulthood. Apart from core symptoms of inattentiveness and hyperactivity-impulsivity there is also cognitive impairment. First choice medication for ADHD is stimulant medication. Despite evidence of safety and efficacy of the stimulant ADHD medications there is poor adherence to prescribed stimulant medication. Guanfacine, an Alpha-2A adrenergic receptor agonist, is a new non-stimulant ADHD treatment option for children and adolescents with ADHD in Europe; authorised since 2015.

**Objective** This literature study will examine the current status of knowledge regarding the safety and efficacy of guanfacine for treating ADHD in children and adolescents between 6 to 17 years old, including long-term use, and how this compares to the other types of medication licensed in Europe for treatment of ADHD for this age group. As a pharmacist, it is important to understand the role of the parents in treatment adherence and which factors to consider when giving patient-counselling.

**Method** A literature search on PubMed and Google was conducted using keywords including: ‘ADHD, guanfacine, methylphenidate, lisdexamfetamine, long-term use, dexamfetamine, atomoxetine, children, adolescent, safety, efficacy, anxiolytic, hypotension, Intuniv, Concerta, ADD, SPD503-318, non-stimulant, and guanfacine authorisation’. Original articles were selected primarily, then the search became widened. Eight original articles, two EMA assessment reports, one EMA summary of procedures, two systematic reviews, one review, one clinical trial result report and one conference poster were selected.

**Results** EMA authorisation of guanfacine is based upon clinical trials conducted by manufacturer Shire. Guanfacine is considered safe and effective for long-term monotherapy treatment for up to 24-months, demonstrating efficacy in improving ADHD symptoms with mild adverse effects. Side-effects include sedation, hypotension and bradycardia. New studies suggest that guanfacine in combination with stimulant medication can improve treatment response and also that guanfacine efficacy is not affected by prior stimulant medication. Lisdexamfetamine was considered to show greatest efficacy amongst ADHD medications (when comparing available data in systematic reviews), yet guanfacine appeared to have greater efficacy than non-stimulant atomoxetine; however, guanfacine had a high incidence of treatment withdrawals due to side-effects. Focus groups and interviews with parents highlighted a fear of adverse effects and academic failure, negative social stigma and risk for substance abuse as factors that influenced their decisions regarding their child's ADHD medication adherence.

**Discussion** The results for efficacy and safety of guanfacine appeared positive across the different studies. There was lack of uniformity in the assessment of the responses and a risk of bias due to subjectivity. There was a lack of studies directly comparing guanfacine to other ADHD medications. Parents have a crucial role in decisions regarding adherence.

**Conclusion** Guanfacine demonstrated efficacy on ADHD symptoms however effect on cognitive ability was inconclusive. Guanfacine has a relatively high incidence of treatment withdrawal due to adverse effects. Support and guidance of parents is critical to address fears regarding ADHD medication and to support the decision-making process.

**Keywords** guanfacine, ADHD, safety, efficacy, children/adolescents
### List of abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADD</td>
<td>Attention deficit disorder</td>
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<td>ADHD</td>
<td>Attention deficit hyperactivity disorder</td>
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<tr>
<td>ADHD-RS-IV</td>
<td>ADHD Rating Scale based on DSM-IV criteria</td>
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<tr>
<td>ATX</td>
<td>Atomoxetine</td>
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<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BUSA</td>
<td>BUSA – National quality register for ADHD-treatment follow-up</td>
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<tr>
<td>CADTH</td>
<td>Canadian Agency for Drugs and Technologies and Health</td>
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<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
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<tr>
<td>CANTAB</td>
<td>Cambridge Neuropsychological Test Automated Battery</td>
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<tr>
<td>CGI-I</td>
<td>Clinical Global Impressions Improvement</td>
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<td>CGI-S</td>
<td>Clinical Global Impressions Severity of Illness</td>
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<tr>
<td>CHMP</td>
<td>The Committee for Medicinal Products for Human Use</td>
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<td>CHQ-PF50</td>
<td>Child Health Questionnaire – Parent Form 50</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>CHQ</td>
<td>Child Health Questionnaire</td>
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<tr>
<td>CPRS-R</td>
<td>Connors’ Parent Rating Scale– Revised</td>
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<td>CPRS-R:L</td>
<td>Connors’ Parent Rating Scale– Revised: Long version</td>
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<tr>
<td>CPRS</td>
<td>Connors’ Parent Rating Scale</td>
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<tr>
<td>CRT</td>
<td>Choice Reaction Time</td>
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<tr>
<td>CTRS-R</td>
<td>Connors’ Teacher Rating Scale - Revised</td>
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<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<td>DSM-IV</td>
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<td>DSM-V</td>
<td>Diagnostic and Statistical Manual of Mental Disorders. 5th edition</td>
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<tr>
<td>DSST/Coding</td>
<td>Digit Symbol Substitution Task/Coding Test</td>
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<tr>
<td>EU-CTR</td>
<td>EU Clinical Trials Register</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>FDA</td>
<td>U.S.A. Food and Drug Administration</td>
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<tr>
<td>GXR</td>
<td>Guanfacine extended-release</td>
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<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
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<tr>
<td>HUI2/3</td>
<td>Health Utilities Index Mark 2 and 3</td>
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<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Health Related Problems</td>
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<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Health Related Problems 10th revision</td>
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<tr>
<td>LDX</td>
<td>Lisdexamfetamine</td>
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<tr>
<td>MPH</td>
<td>Methylphenidate</td>
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<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
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<tr>
<td>MSS</td>
<td>Medical Satisfaction Survey</td>
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<tr>
<td>NHS</td>
<td>National Health Service (United Kingdom)</td>
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<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<tr>
<td>NYPRS-S</td>
<td>New York Parent’s Rating Scale-School-aged</td>
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<td>PERMP</td>
<td>Permanent Product Measure of Performance math test</td>
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<tr>
<td>PGA</td>
<td>Parent Global Assessment</td>
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<tr>
<td>PSS</td>
<td>Pictorial Sleepiness Scale</td>
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<tr>
<td>PSI/SF</td>
<td>Parent Stress Index-Short Form</td>
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<td>SNAP-IV</td>
<td>Swanson, Nolan and Pelham Teacher and Parent Rating Scale</td>
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<tr>
<td>SWM</td>
<td>Spatial Working Memory</td>
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<tr>
<td>WFIRS</td>
<td>Weiss Functional Impairment Rating Scale</td>
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<tr>
<td>WFIRS-P</td>
<td>Weiss Functional Impairment Rating Scale-Parent Report</td>
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</tbody>
</table>
# Table of contents

Abstract ............................................................................................................ I  
List of abbreviations and acronyms ................................................................. III  
1. Introduction .................................................................................................. 1  
   1.1 ADHD symptoms, prevalence, diagnostic criteria, pathophysiology .......... 1  
   1.2 ADHD treatment guidelines for children and adolescents ..................... 2  
   1.3 Long-term ADHD medication ................................................................. 3  
   1.4 Parental role in decisions regarding ADHD pharmacotherapy .............. 3  
   1.5 Guanfacine extended-release, a new treatment for ADHD .................... 4  
      1.5.1 History of authorisation of Intuniv ................................................. 4  
      1.5.2 Mechanism of action of guanfacine and other ADHD medications ...... 4  
   1.6 Clinical evidence of the safety and efficacy of guanfacine .................... 5  
      1.6.1 Efficacy outcome measures ............................................................. 5  
      1.6.2 Interactions ...................................................................................... 6  
      1.6.3 Side-effects .................................................................................... 6  
      1.6.4 Comparison of guanfacine with other ADHD medications ............. 6  
      1.6.5 Transition from stimulant to guanfacine ........................................ 6  
   1.7 Possible new areas of use for guanfacine ............................................. 6  
2. Objective .................................................................................................... 7  
3. Method ....................................................................................................... 7  
   3.1 Selected results for further analysis ...................................................... 10  
4. Results ....................................................................................................... 11  
   4.1 Efficacy of guanfacine at time of authorisation in Europe .................... 11  
      4.1.1 European public assessment report (EPAR) for Intuniv, primary studies .. 11  
      4.1.2 European public assessment report (EPAR) for Intuniv, secondary studies 12  
      4.1.3 A systematic review and meta-analysis, (Ruggiero et al, 2014) (21) .......... 13  
   4.2 Safety of guanfacine at time of authorisation in Europe ....................... 15  
      4.2.1 European public assessment report (EPAR) for Intuniv, safety concerns .. 15  
      4.2.2 Treatment discontinuation ............................................................... 15  
      4.2.3 Safety reported in systematic review by Ruggiero et al (2014)(21)........... 16  
      4.2.4 Risk-benefit .................................................................................. 16  
      4.2.1 Safety update post-authorisation ..................................................... 16  
   4.3 Long-term studies .................................................................................. 17  
      4.3.1 Long-term study 318 results ......................................................... 18  
   4.4 Recently published articles since authorisation .................................... 20  
      4.4.1 Results: Cognitive effects of treatment ......................................... 20  
      4.4.2 Results: Combined Guanfacine and stimulant treatment comparisons .. 21  
      4.4.3 Results: Guanfacine efficacy following prior methylphenidate treatment . 21  
   4.5 Comparison of efficacy and safety of guanfacine with other ADHD medications 23  
   4.6 Role of Parents in decisions regarding child ADHD medication ........... 24  
5. Discussion .................................................................................................. 26  
   5.1 Discussion: method .............................................................................. 26  
   5.2 Efficacy ................................................................................................ 26  
      5.2.1 ADHD symptoms ........................................................................ 27  
      5.2.2 Functioning .................................................................................. 28  
      5.2.3 Cognitive effect ........................................................................... 28  
      5.2.4 Effect of prior stimulant treatment on guanfacine efficacy ............. 28  
      5.2.5 Long-term efficacy ....................................................................... 29  
   5.3 Safety .................................................................................................... 29  
      5.3.1 Long-term safety ........................................................................ 30  
   5.4 Comparison of ADHD medications ................................................... 30  
   5.5 Parental role in ADHD treatment decision-making ............................ 31  
      5.5.1 Study design ................................................................................ 31  
      5.5.2 Parental concerns ....................................................................... 32
1. Introduction

ADHD is a condition that affects children and their families and society as a whole. It is important to be able to find treatments that are safe and effective and to be able to improve the quality of life for the patients and their families. There is a need to find safe and effective ADHD medication for children and adolescents and medications that are non-stimulant may provide an alternative to stimulants, potentially reducing the risk for addiction and abuse.

Guanfacine, a non-stimulant, is a new treatment option for ADHD in Europe and as a pharmacist it is important to be up to date with current status of knowledge regarding the efficacy and safety of this treatment in order to be able to give advice to patients and parents of the child patients.

Despite evidence of safety and efficacy of ADHD medications and the importance to treat individuals with ADHD there is a significant proportion of ADHD patients with poor adherence to prescribed medication (1). Pharmacists have a central role in patient counselling as they can meet the parents of the child patients possibly more regularly than the medical specialists. It is therefore important for pharmacists to also be aware of factors that influence these parents, particularly with regard to decisions and questions related to the commencement of, assessment of, adjustments to and adherence to ADHD treatment in order to offer best support and guidance to them.

1.1 ADHD symptoms, prevalence, diagnostic criteria, pathophysiology

ADHD is a complex heterogeneous neurodevelopmental and neurobehavioural disorder characterised by persistent age-inappropriate hyperactivity-impulsivity and/or inattentiveness (2). ADHD has been estimated to affect approximately 5% of school children worldwide, without significant regional differences (3).

ADHD is diagnosed by specialist medical health professionals using either the American Psychiatric Association’s DSM diagnostic system or World Health Organization’s ICD criteria; both criteria are valid for use internationally (3). Interviews with the child, parents and child’s schoolteachers contribute to assessing and identifying the ADHD symptoms (4). The DSM-V details three different presentations of the core ADHD-symptoms (previously referred to as ‘ADHD subtypes’ in DSM-IV) (5); predominantly inattentive, predominantly hyperactive-impulsive and combined inattentive-hyperactive-impulsive and also the severity can be specified as either mild, moderate or severe. In order to meet the diagnostic criteria for ADHD, these ADHD symptoms need to have been present before 12 years of age and ADHD can continue into adolescence and adulthood (4). For the diagnosis of ADHD in Sweden, health professionals use the DSM-V diagnostic criteria and in United Kingdom (UK) the guidelines specify that both diagnostic systems are used; DSM-V (ADHD) and ICD-10 (hyperkinetic disorder; HKD) (4, 6).

Apart from the core ADHD symptoms of inattentiveness and hyperactivity-impulsivity, patients also suffer from cognitive impairments including short-term memory deficiency and also problems with regulating sensory stimuli and emotional expression, resulting in an impaired quality of life for the individual and their families (7). ADHD-symptoms which present in individuals vary over time and present differently in different age groups (8).
The aetiology of ADHD is not fully known, yet there appears to be a strong genetic link associated with the pathophysiology of ADHD (7). ADHD is considered to be a neurological disorder relating to the prefrontal cortex which regulates cognitive functions, however, more recently ADHD is considered to affect the whole brain (2). ADHD appears to be associated with a delayed brain maturation, resulting in neural dysfunction and therefore possibly causing dysregulation of neurotransmitter systems, particularly dopamine and noradrenaline (2).

1.2 ADHD treatment guidelines for children and adolescents

Apart from non-pharmacological interventions, treatment for ADHD can also include pharmacotherapy for which CNS stimulants remain the first choice medication in USA and Europe (9, 10).

The ADHD treatment guidelines vary in the different European countries. The medications licensed to treat children and adolescents aged 6-17 years with ADHD in Sweden and UK are methylphenidate, dexamfetamine, lisdexamfetamine (all CNS stimulants) and non-stimulants atomoxetine and guanfacine (11, 12). In the UK and Sweden first choice medication for children and adolescents with ADHD is the stimulant medication methylphenidate or if Tourette’s syndrome, tics, anxiety disorder, sleep disorder or risk for stimulant abuse are present then non-stimulant atomoxetine is the alternative medicine of first choice (11, 13). If treatment response to first-line medication is not successful due to side-effects or lack of improvements to symptoms then second choice for ADHD medication in UK for treating children and adolescents is dexamfetamine (12). In Sweden, if first choice was methylphenidate second choice would be either lisdexamfetamine or atomoxetine (11). If atomoxetine was first choice then methylphenidate would be second choice before selecting lisdexamfetamine in Sweden. Also treatment guidelines state that dexamfetamine is also licensed however special consideration must be taken due its immediate release formulation which has an inherent increased abuse potential compared to extended release or prodrugs (11). Third choice medication in Sweden and UK is guanfacine extended release when treatment with stimulant medication has been unsuccessful or is unsuitable (6, 11).

Methylphenidate dominates prescribing in Europe, accounting for over 80% of ADHD medications prescribed in Sweden, with adolescents aged between 10-17 years old having the highest prescribing rate; 4.5% of boys and circa 2% of girls in this age group (14, 15). Methylphenidate has been prescribed for many years for ADHD patients and is well studied, hence is first-choice medication for ADHD (16).

ADHD medication use in USA is highest in 10-14 year olds at 8.8% (14), with amphetamines almost prescribed as often as methylphenidate. ADHD medication use is greater in USA, however, there has been a substantial increase in ADHD medication prescribing in European countries during the last decade (14).

Before ADHD pharmacotherapy is commenced the children/adolescents require a medical examination to check blood pressure, heart rate, also to check the child’s growth and weight against a growth chart (11, 13). Psychiatric co-morbidities, risk for substance abuse, epilepsy, and family history of serious cardiovascular disease need to be taken into account when assessing suitability for ADHD medication and further medical assessment tests may be required (11, 13).

Regular medical patient check-ups to assess the effect of the treatment, also to measure blood pressure, heart rate, height and weight need to be undertaken. Annual assessment of ADHD medication treatment is required, with the possible withdrawal of treatment to assess if treatment is still required and also to have a break in treatment to temporarily reduce side-effects (11, 12, 17). To determine the optimal treatment and dose the patient
is required to take the medicine over an agreed period of time and for the effects and adverse events to be assessed at check-up with the medical specialist, often consulting with parents and reports from school to determine the effect and suitability of the treatment (11, 18).

An evaluation of the severity of the ADHD symptoms can be made before treatment commences using the rating scales Clinical Global Impression - Severity Scale (CGI-S) which rates symptom severity or Swanson, Nolan and Pelham Teacher and Parent Rating Scale (SNAP-IV) (a behavioural questionnaire). Upon follow-up consultation, the Clinical Global Impression – Improvement scale (CGI-I) can be used to rate improvement in symptoms and can be therefore used to track response to the ADHD medication (11).

1.3 Long-term ADHD medication

ADHD is a chronic condition which can continue from childhood through to adulthood, with long-term ADHD medication for the patient. Previously, most clinical studies were based on short-term ADHD-medication, with studies shorter than 6 months in duration, however recent studies have focused on long-term effects over 24 month periods (9). Although both stimulant and non-stimulant ADHD medications have been shown to be continuously effective over 24 months with adverse events that are considered mild and generally well tolerated, there are important medical checks required to assess risks and benefits in continuation of treatment (9).

The main adverse effects of ADHD medications which are of concern for long-term ADHD stimulant medication are decreased appetite, anorexia, nausea, insomnia, negative effects on growth and weight, cardiovascular effects and risk for substance abuse (9). Non-stimulant atomoxetine and guanfacine do not carry the risk for potential substance abuse yet atomoxetine can affect growth and weight negatively whereas guanfacine can cause weight increases (9, 11). Treatment with atomoxetine or stimulant ADHD medications increases both systolic and diastolic blood pressure and increases heart frequency; whereas, guanfacine reduces heart rate and blood pressure and can cause sedation (11). The stimulant ADHD medications and non-stimulants atomoxetine and guanfacine all can cause adverse psychiatric effects including depressive disorders, suicidal thoughts and mood disorders. As such, this is an important factor when assessing the suitability of ADHD medication for an individual and needs to be monitored over time (9, 11).

1.4 Parental role in decisions regarding ADHD pharmacotherapy

During the procedure for diagnosing children with ADHD, parents are involved in rating the ADHD symptoms of their children via interviews and questionnaires (4). Parents’ ratings are taken into account alongside ratings given by schoolteachers and the medical specialist conducting the investigation (4).

Parents also have a key role in deciding on whether or not to proceed with ADHD medication recommended for their child and also are key in ensuring their child’s adherence to the medication over time (19). Another important factor is that the parent has a responsibility to report changes in their child’s behaviour over time to medical professionals and to contribute to the assessment of whether the treatment is adequate, which is compounded by the fact that the parents’ expectations for results may be very different from the actual results possible (19). This literature review will explore parental attitudes and influential factors that affect children’s adherence to ADHD medication.
1.5 Guanfacine extended-release, a new treatment for ADHD

Intuniv (extended release guanfacine, GXR) is an extended-release tablet containing guanfacine hydrochloride (1 mg, 2 mg, 3 mg, 4 mg) which is administered once daily and is manufactured by the pharmaceutical company Shire (3). Guanfacine was originally available as a centrally acting antihypertensive (20, 21).

1.5.1 History of authorisation of Intuniv

Shire first submitted a new drug application to U.S. Food & Drug Administration (FDA) for Intuniv (guanfacine) extended release 1 mg, 2 mg, 3 mg and 4 mg tablets in August 2004 and approval was granted for Intuniv in USA on 2nd September 2009 with the indication to treat ADHD as monotherapy in children and adolescents aged 6 – 17 years (22). Shire was then requested by FDA to conduct a further clinical trial focused on the efficacy in the adolescent group aged 13 – 17 years due to the trial data available at time of authorisation failing to show efficacy in that age group; however, this was deemed to be possibly related to inadequate exposure, so authorisation of Intuniv was not delayed for this age group (22). In April 2010 Shire submitted an application to FDA together with supportive clinical studies in order to seek market approval for Intuniv as an adjunctive treatment of ADHD with oral stimulants for children and adolescents aged 6 – 17 years; this was then granted on 25th February 2011 (23).

Shire then later applied to Canada for authorisation of Intuniv as monotherapy for children aged 6-12 years and also as adjunctive to stimulants for 6 – 12 year olds that had a suboptimal response to stimulants alone; authorisation was granted on 5th July 2013 (3). On 24th June 2016 the indication for use in Canada had been changed to treatment of ADHD for 6 – 17 year olds as monotherapy or as adjunctive to stimulants for 6 – 17 year olds (24).

On 3rd March 2014, shortly after completion of a clinical trial that satisfied EMAs regulatory requirements, Shire submitted an application to EMA for centralised European authorisation of Intuniv as monotherapy for the treatment of ADHD in children and adolescents aged 6 – 17 years (3). Intuniv was authorised in Europe on 17th September 2015 as monotherapy for ADHD in children and adolescents aged 6 – 17 years old ‘for whom stimulant medication is not suitable, not tolerated or have been shown to be ineffective’, and is currently under additional monitoring (3, 25). Intuniv was then launched in UK in February 2016 (26).

1.5.2 Mechanism of action of guanfacine and other ADHD medications

The mechanism of actions of ADHD medications is not fully understood, however there are hypotheses of the probable mechanism of action (2).

Guanfacine is a selective Alpha-2A adrenergic receptor agonist which has been shown to improve cognitive function in the prefrontal complex (2). The mechanism of action of guanfacine in ADHD treatment is not known; however, it is hypothesized that guanfacine directly stimulates Alpha-2A adrenergic receptors in post-synaptic neurons. The consequent closing of hyperpolarisation-activated cyclic nucleotide-gated (HCN) channels allows increased synaptic inputs to neuron, increasing the strength of the noradrenaline neurotransmission, thus strengthening cognitive function (2).
Methylphenidate and amphetamines block noradrenaline and dopamine presynaptic transporters and increase levels of these neurotransmitters. Atomoxetine is a non-stimulant that operates by blocking the presynaptic noradrenaline transporters and indirectly stimulating a moderate increase in dopamine and noradrenaline in the prefrontal cortex (2).

1.6 Clinical evidence of the safety and efficacy of guanfacine

The Shire sponsored clinical trials behind the authorisation of Intuniv in Europe included the trials which were detailed in the earlier prior authorisation clinical review documents for Intuniv in USA and Canada and also included more recent trials with a European focus (3, 27, 28). The European public assessment report for Intuniv represents the most recent clinical review of Intuniv and is the starting point for this literature review when looking at the currently accepted knowledge of the safety and efficacy of guanfacine when treating ADHD in children and adolescents (3). The European public assessment report for Intuniv included 5 pivotal efficacy randomised double-blind placebo-controlled phase III trials and eight supportive studies (6 phase III trials and 2 phase II trials) which included two long-term open label extension studies. A third long-term study was to form the basis of the application yet has not yet been published; study ID 318 (3). Study 318 trial results will be analysed in this literature review as the study is now complete and the clinical results are available, however this trial is yet to be published.

There is a systematic review of the safety and efficacy of guanfacine written by Ruggiero et al (2014) (21) which is independently written and not sponsored by Shire. This review will serve as an alternative review to compare with the European public assessment report for Intuniv. Three of the pivotal trials covered in the European public assessment report are included in this systematic review and three of the supportive studies are also included (21). An older study independently written without funding from Shire is also included in this systematic review.

Most of the safety and efficacy studies for guanfacine and the related published articles are funded by the manufacturer Shire and this includes all the studies which are the basis for the authorisation of guanfacine in Europe, USA and Canada. Thus, this literature study will use articles which are both sponsored by Shire and also includes recent studies and reviews which are independent from Shire funding.

1.6.1 Efficacy outcome measures

The outcome measures to assess efficacy used in the clinical trials included rating scales which assessed the severity of ADHD symptoms at baseline and at end of the trial and also changes in executive function and quality of life. ADHD-RS-IV (ADHD rating scale) is a scale used in many of the clinical trials and corresponds to the DSM-IV diagnostic criteria for ADHD and is administered by a teacher or parent. CGI-I is also a commonly used tool in the trials which measures the patient’s global improvement in their symptoms. Also widely used, CGI-S is a clinical judgement of the patient’s overall condition. CPRS-R:L is an assessment scale administered by parents which includes DSM-IV subscales to assess ADHD symptom severity. WPIRS-P is a scale administered by the parent to assess functional impairment in different domains including at home, at school and social activities (3, 29).
1.6.2 Interactions

Guanfacine is metabolised via CYP3A4/5 enzymes and therefore interactions occur with medications or foods that are inducers or inhibitors of CYP3A4/5 enzymes, thereby affecting plasma concentrations of guanfacine. Guanfacine absorption increases if administered with high fat meals and therefore it is recommended to avoid high fat food intake at time of guanfacine administration (3). Caution needs to be also taken if the patient also has medication to lower heartrate or to prolong QT-interval (3).

1.6.3 Side-effects

The main side-effects for guanfacine reported in the European public assessment report for Intuniv were hypotension, bradycardia, syncope, risk for pro-arrhythmic effect, weight gain, sedation and somnolence. Guanfacine treatment should not be abruptly terminated due to the risk of increased blood pressure and heart frequency; instead careful downward titration of dose together with monitoring blood pressure and heart rate is recommended (3).

1.6.4 Comparison of guanfacine with other ADHD medications

There is a lack of head-to-head comparison trials to directly compare guanfacine with other ADHD medications and therefore review documents indirectly comparing the effects of guanfacine with other ADHD medications will be used in this literature review in order to provide an initial understanding in this area; an independently funded review and a drug manufacturer funded review have been selected.

1.6.5 Transition from stimulant to guanfacine

Guanfacine is likely to be prescribed for patients that have previously been taking stimulant medication and there are certain practical aspects to consider. The course of action is determined by the response to the stimulant medication. If there were severe adverse events caused by stimulant medication, or no clinical effect experienced, then this needs to be terminated immediately and guanfacine commenced as monotherapy, with careful slow dose titration until optimal dosing is achieved (usually a maintenance dose of 0.05-0.12 mg/kg/day) (3, 29, 30). If the stimulant medication has significant clinical effect in the individual then the treatment is continued and guanfacine added gradually to the stimulant medication; this is important as there is a delay in the time taken to achieve clinical response to guanfacine, and therefore, it is important to maintain the stimulant medication during this period (29).

A newly published article (Huss et al, 2016)(31) featuring separate analysis of two Shire trials with regard to the efficacy of guanfacine following methylphenidate treatment is included in this literature review; this is an important area to explore as this is commonly the case that patients have had prior exposure to methylphenidate before guanfacine treatment.

1.7 Possible new areas of use for guanfacine

There are recent studies emerging which have looked at the feasibility of guanfacine as an anxiolytic in patients with post-traumatic stress disorder and anxiety disorders (32, 33). There are also recent studies assessing the use of guanfacine in treating ADHD in
paediatric patients with autism (34, 35). There is also research looking at the effect of guanfacine on children and adolescents in different age groups and with different presentations of ADHD (36). However, in the EMA assessment report it was stated that no specific ADHD population had been identified as a subset of patients that would benefit most from guanfacine treatment (3). This area of study may develop over time to present new treatment areas for guanfacine in the future, yet this is still at an early stage.

2. Objective

The use of non-stimulant medication guanfacine in the treatment of ADHD in children and adolescents is a new area that requires monitoring. It is important as a pharmacist to understand and monitor the studies regarding efficacy and safety of this medication for this patient group in order to be able to give advice and information to the patients and parents of the patients:

- receiving this new treatment
- considering changing their ADHD treatment
- considering treatment initiation or termination.

Is guanfacine safe and effective for treating ADHD in children and adolescents between 6 to 17 years of age, including long-term use? How does guanfacine compare with other ADHD medicines licensed in Europe for this age group? Which factors influence the parental decisions regarding ADHD pharmacotherapy for their child? And how can pharmacists address the informational and guidance needs of these parents to enable better support and understanding of their child’s medication?

3. Method

For this literature study searches were initially conducted on 1st March 2017 using the search terms ‘ADHD’ and ‘guanfacine’ on the following websites: ema.europa.eu (European Medicines Agency, EMA), socialstyrelsen.se (Socialstyrelsen, The Swedish National Board of Health and Welfare) and lakemedelsverket.se (Läkemedelsverket, Swedish Medical Products Agency).

During 3rd – 5th April 2017 PubMed searches were conducted (see Appendix A) which firstly were limited by applying a filter to show articles which were published in the last two years—the period during which guanfacine has been available for ADHD treatment in Europe. Free text searches and not exclusively MeSH terms were included in order to be able to obtain newer articles which may not yet have been indexed with MeSH terms. Searches for articles published in the last five years were also included in order to widen the search to include important studies which would have been available when considering guanfacine as an ADHD treatment in Europe (see Appendix A).

Following feedback from my supervisor on 6th April 2017 after the first searches were conducted, certain clinical studies were identified as relevant studies for the base of the results analysis, due to their relevance to the objectives of this literature review. These studies were then read in full and summarised in order to identify which information was missing.

Further searches were then conducted on PubMed with the search terms ‘ADD and guanfacine’, ‘attention deficit disorder and guanfacine’, ‘Intuniv’ and ‘Concerta and Intuniv’ on 10th - 11th April 2017 (see Appendix A). The searches were not limited by applying filters in order to find earlier studies relating to guanfacine being authorised in US, and also to pick up trials specific only to ADD that may have been missed. Concerta
was chosen when searching for comparison trials with Intuniv, as Concerta is the brand name for methylphenidate, which was identified as the most commonly prescribed medication for ADHD in Sweden and UK (12, 14).

Original articles were selected primarily from the PubMed search results, then the search became widened in order to have more background information and to be able to read systematic review articles. Selections were subsequently made based on the titles; titles referring to guanfacine treatment of ADHD in children and adolescents with a focus on safety and efficacy were included. Certain studies excluded from the search results were not of relevance to the objectives of this literature study. Exclusion criteria included: studies not specific to safety and efficacy of guanfacine; studies which specified a focus on adults with ADHD; studies mainly focused on co-morbidities; studies not written in English or Swedish; studies based on singular case studies; and papers based on rodent studies. Only review articles written after guanfacine was authorized in US in 2009 for treating paediatric ADHD patients were included in the selected articles from the wider searches conducted 10th – 11th April 2017 (see Appendix A). The abstracts of each selected article were then read to further assess their relevance and to ascertain if the articles were to be included in the literature review. The articles were then summarised and categorised as to the type of article and to which area of the literature review they related.

Further literature searches were conducted (9th – 12th April 2017) following feedback received from my supervisor. Between 9th – 11th April 2017 medicines.org.uk (electronic Medicines Compendium, eMC) and Fass.se websites were checked to find out brand names for the medicines which are licensed to treat ADHD paediatric patients in Sweden and in UK. Searches were then conducted with search terms ‘ADHD’, ‘Intuniv’ and ‘guanfacine’ on Ema.europa.eu, Fda.gov (U.S. Food & Drug Administration, FDA), Shiretrials.com, nice.org.uk, gov.uk (NICE) websites. The new search results were categorised as to which area of the literature review they related and subsequently read and summarised in order to select which articles were of most importance regarding safety and efficacy, prioritising original articles.

On 9th April 2017 the UK’s NHS Choices website (nhs.uk) was searched using ‘ADHD’ as a search term in order to find the medicines that are licensed to treat child ADHD patients in UK. Via the NHS Choices website a link to (National Institute for Health and Care Excellence) NICE website was then found which had information on ADHD treatment in the UK. The NICE website was then searched, using ‘guanfacine’ as a search term, and an evidence summary was found. The guanfacine safety and efficacy clinical trials which were referenced in the evidence summary on NICE, and those which were not already duplicates of articles found in previous PubMed searches, were then added to the list of selected articles. Medicines & Healthcare products Regulatory Agency website (gov.uk) was then searched by using ‘ADHD’ as a search terms in order to search for medicines licensed to treat ADHD in children in United Kingdom.

On 11th April 2017 a search was conducted on google.com (Google) using the search terms ‘shire pharmaceuticals guanfacine study’ and the clinical trials that were sponsored by Shire, the manufacturer of Intuniv, were found. A search was then conducted on the FDA website with search term ‘guanfacine’ to access background documentation regarding the clinical studies from which guanfacine was approved in USA. A further search on Google was conducted with search term ‘fda guanfacine’ resulting in finding a clinical review of guanfacine hydrochloride on fda.gov (US Food & Drug Administration, FDA) website. A search was then conducted on the FDA website using the search term ‘guanfacine’ to access background documentation regarding the clinical studies from which guanfacine was approved in USA. A search on Google was then made using search term ‘fda guanfacine’ and a clinical review of guanfacine hydrochloride on US Food & Drug Administration (FDA) website was found.
On 12th April 2017 a PubMed review by Canadian Agency for Drugs and Technologies and Health (CADTH) was found after searching for ‘SPD503-315 reference’ on Google and from this online review a link to CADTH website cadth.ca was found; once on CADTH website a Clinical Review Report for Intuniv was found after searching for ‘ADHD guanfacine’.

By searching on Shiretrials.com for the clinical trials and then linking from there to ClinicalTrials.gov on 14th April, details about publications of the trials results could be seen. The search results that had already been found could then be linked against their study ID numbers which they are referred to in the authorisation documents. In order to access the recent results of study SPD503-318 which was also sponsored by Shire and assessed long term safety and tolerability of guanfacine, ‘SPD503-318’ was searched for on clinicaltrialsregister.eu (EU Clinical Trials register); SPD503 is extended release guanfacine; 318 is the study ID. A search was then conducted on Google, using search term ‘SPD503-318’ and a summary of the outcomes of the study SPD503-318 was found on Researchgate.net website.

On 19th April 2017 a search was conducted on Google using search terms ‘parents deciding ADHD medication child’ and two original articles written within the last five years focused on parental decisions regarding ADHD pharmacotherapy for their child were selected. A search on PubMed was then conducted using free text search terms ‘parent decide ADHD’ and by reading the title and abstract an article which specifically related to parental influence in the child’s ADHD pharmacotherapy was selected (see Appendix A). A further search on Google was then conducted using search terms ‘transition stimulant to nonstimulant adhd’ in order to find information on the transition period when changing from stimulant therapy to guanfacine.

On 24th April 2017 a link to a further long-term phase 4 study was found by linking from the Evidence Summary (6) on Nice.org.uk website and also further documents were found on cadth.ca website after using search term ‘Intuniv’.

On 27th April 2017 a Google search was conducted using the terms ‘guanfacine authorisation’ and a link was found to sps.nhs.uk website (the NHS Specialist Pharmacy service) which had an overview of the authorisation process for Intuniv and links to the FDA and EMA. On 28th April 2017 a search was conducted through the authorisation documentation on ema.europe.eu (EMA), fda.gov (FDA), nhs.uk (NHS) and cadth.ca (CADTH) websites to try to compile a history of the authorisation process and to be able to speculate as to the reasons behind the later authorisation of Intuniv in Europe and the differences in licensing across USA, Canada and Europe.

The studies which were selected after the later searches were all read through and summarised in order to ascertain which articles were to be the main focus of the review. Certain studies were also discarded at this stage due to being peripheral to the objectives of this review. Some additional studies on efficacy trials were then added to my search results which were referred to in review documents.

The PubMed literature searches resulted in a total of 519 search results, of which 53 unique results were selected as relevant for inclusion in both the results and in the introduction (see Appendix A).
3.1 Selected results for further analysis

The formal European public assessment report for Intuniv (EMA, 2015) which formed the basis for authorisation of Intuniv in Europe was selected as a start point for the in depth analysis of the safety and efficacy of guanfacine, as it is the most recent clinical review document and includes the trials from the earlier authorisation documentation in USA and Canada. The results from an independently funded systematic review of the safety and efficacy of guanfacine by Ruggiero et al (2014) was also selected to form an alternative start point for the analysis.

In order to present updated information on the long-term safety and efficacy of guanfacine, the two long-term studies SPD503-305 (Sallee et al, 2009) and SPD503-303 (Biederman et al, 2008) which were included as supportive studies in the European public assessment report for Intuniv (EMA, 2015) were selected for this analysis. In order to present the findings of the latest unpublished long-term study, SPD503-318, which was conducted post-authorisation in order to comply with EU regulations, the following were selected: the EMA assessment report of this paediatric study (EMA, 2016), the EU Clinical Trials Register results for SPD503-318 (EU Clinical Trials Register, 2016) and a conference poster presentation at the 29th European College of Neuropsychopharmacology (ECNP) Congress (Huss et al, 2016).

To address new knowledge regarding efficacy and safety of guanfacine published since authorisation, two recently published original articles were selected based on a non-manufacturer funded clinical trial. One article looked at cognitive function based on combined stimulant and guanfacine treatment (Bilder et al, 2016) and the other article compared efficacy of combined stimulant and guanfacine treatment to monotherapy (McCracken et al, 2016). A newly published analysis which focuses on guanfacine efficacy post-stimulant treatment has been selected (Huss et al, 2016) and is based upon two of the primary efficacy trials sponsored by Shire (SPD503-315 and SPD503-316) which were included in the European public assessment report for Intuniv (EMA, 2015). The EPAR – Procedural steps and scientific information after authorisation for Intuniv (EMA, 2017) was also selected to include post-authorisation updates in safety information.

No clinical trials have been conducted which directly compare the efficacy and safety of guanfacine to other ADHD-medications except for a short-term study which had an atomoxetine arm included as reference data against placebo. Instead the conclusions from a new systematic review funded by Shire (Joseph et al, 2017) and a recent independently funded new review (Gao et al, 2016) which compare ADHD-medications were selected.

The three original articles in the search results which focused on parental influence over ADHD-treatment decisions were also selected (Cormier, 2012), (Coletti et al, 2012) and (Ahmed et al, 2017).

In total, this literature review is based upon eight original articles, two EMA assessment reports, one EMA summary of procedures, two systematic reviews, one review, one clinical trial result report and one conference poster.
4. Results

4.1 Efficacy of guanfacine at time of authorisation in Europe

The European public assessment report (EPAR) for Intuniv (3) is a report written by EMA which includes a safety and efficacy assessment which was the basis for central authorisation of guanfacine treatment of ADHD in Europe. This assessment report and a systematic review, Guanfacine for attention deficit and hyperactivity disorder in paediatrics: A systematic review and meta-analysis (21) written independently of Shire by Ruggiero et al in 2014 will provide an overview of the information known about the efficacy and safety of guanfacine at time of authorisation in Europe.

4.1.1 European public assessment report (EPAR) for Intuniv, primary studies

European public assessment report (EPAR) for Intuniv (3) was based on clinical trials funded by Shire and was written by EMA in 2015 at the time of authorisation of guanfacine in Europe. The efficacy and safety of guanfacine was based on the clinical trial evidence of five primary efficacy studies which were all randomised, placebo controlled, multicentre parallel group studies. There were also seven supportive studies which were discussed and one further supportive study (study ID: 318) was mentioned that was still ongoing at time of the authorisation (Table 1).

To participate in the Shire sponsored studies, the patients were required to have an ADHD diagnosis according to DSM-IV without any co-morbidities, except for Oppositional Defiant Disorder (ODD) which was permitted for inclusion. Among the five pivotal trials in EPAR (3) were two short-term dose response studies, two short-term flexible dose studies and one randomised withdrawal study. All of the trials included in the report had patients within 6 – 17 years age except for trial 312 which had patients that were aged 13 – 17 years old (Table 1).

The pivotal studies in EPAR all had ADHD-RS-IV symptom rating scale as the primary endpoint to measure outcomes, however studies 312, 315 and 316 had secondary endpoints, WFIRS-P and CGI-I, to measure global functioning (3).

The pivotal studies had a high dropout rate. The highest drop-out was in study 316, which had an active controlled arm with atomoxetine; a 52% dropout rate for the guanfacine active arm with 30% of these drop-outs occurring within the first treatment month (3). The primary reason behind drop-out for the patients treated with guanfacine was treatment failure which was defined as having two of the following criteria at two subsequent visits after baseline : ≥ 50% increase (worsening) in the total ADHD-RS-IV score, ≥ 2 point increase in CGI-I score or if the test subject discontinued the treatment (3).

The overall mean effect size (difference from placebo on ADHD-RS-IV scale) with regard to guanfacine seen in the pivotal studies in EPAR was 0.5 – which is a smaller effect size than mean effect sizes seen in methylphenidate (MPH) studies which have varied between 0.5 – 0.9 (3). The effect size was highest in the study with the atomoxetine active arm, study 316, with 0.7 for guanfacine and 0.3 for atomoxetine (3).

There was no effect recorded for the adolescents (13 – 17 year olds) that took part in the mixed age group pivotal studies (study 301, 304, 315 and 316). The study 312 which only had adolescent test subjects was the only study that showed an effect for this age group with an effect of 0.5 demonstrated. Shire was reported to have explained this as a
consequence that the guanfacine dose had previously been too low for the older children, also that the sample sizes were small and the placebo response had been high in studies 315 and 316. Shire also gave reassurances by giving early indications of the progress of the long-term study 318 which was ongoing at the time of authorisation, with preliminary data that ADHD-RX-IV total scores were comparable between adolescents and children (3).

There were indications that the results of the pivotal fixed dose studies 301 and 304 demonstrated statistically significant effect for the combined ADHD subtype and a lesser and non-statistically significant effect for the inattentive subtype. Data was then analysed by Shire to see if sedation contributed to the effect of guanfacine in ADHD patients, by stratifying the results into patients who did or did not have sedation as a reported adverse effect. This analysis regarding the effect of sedation on the ADHD-RS-IV effect did not provide any conclusive results. Data did however show that guanfacine had shown efficacy in individuals that did not experience sedative adverse events, with similar results for both the combined and inattentive subtypes (3).

The secondary outcomes in study 312, 315 and 316 (the effect on global functioning) demonstrated that only study 316 had statistically significant results. However data that was analysed from studies 312 and 316 observed that the ADHD patients that had reported sedation as an adverse effect had a negative impact on their global functioning (3).

4.1.2 European public assessment report (EPAR) for Intuniv, secondary studies

Study 307, which was a dose optimisation study for children ADHD patients aged 6-12 years that also had oppositional symptoms, this was a randomised, double-blind, multicentre and placebo-controlled study. The results demonstrated a statistically significant improvement of oppositional symptoms measured with the CPRS-R:L scale and the effect size was 0.6 (3).

Studies 313, 314 and 206 were randomised, double-blind, multicentre, placebo-controlled studies.

Study 313 was to assess the effect of guanfacine as an adjunct to long-acting psychostimulant ADHD medications in patients that had shown only partial response to psychostimulant medicines; the study results suggested that there was a greater improvement in ADHD-RS-IV with the patients that were treated with the adjunctive guanfacine compared to adjunctive placebo, however there were no efficacy of global functional outcomes measured.

Study 314 was a study designed to compare the efficacy of either morning or evening administration of guanfacine. The results showed improvements in both the morning and evening administration groups, with no differences between the two groups; these improvements included both on the ADHD-RS-IV ADHD symptom scale and the WFIRS-P global functioning scale.

Study 206 aimed to assess the cognitive effects of guanfacine treatment compared with placebo over 6.5 weeks of treatment. There were no significant differences compared to placebo reported. The sedative effect of guanfacine was considered to have a negative impact on tasks that required clarity of thought; however, the positive effect of guanfacine on cognitive ability through reducing the ADHD-symptoms results in it being difficult to forecast the cognitive effect with guanfacine treatment (3).
Studies 303 and 305 were long-term open-label extension studies of the short-term studies 301 and 304/205 respectively and were designed to assess the long-term efficacy of guanfacine over 24 months. However, concerns were raised due to the drop-out rate being circa 80%, however, the 20% that completed the long-term studies demonstrated long-term efficacy in these patients.

4.1.3 A systematic review and meta-analysis, (Ruggiero et al, 2014) (21)

A systematic review of the evidence of guanfacine safety and efficacy written by Ruggiero et al (2014) (21) was funded independently of Shire and was published shortly before the authorisation of Intuniv in Europe.

Guanfacine for attention deficit and hyperactivity disorder in paediatrics: A systematic review and meta-analysis (21) was based on seven randomised controlled trials, six of which were included in EPAR (EMA, 2015)(3) (Table 1).

The CGI-I score was used in the meta-analysis as an outcome measure for treatment response across the seven studies. ADHD-RS-IV scores were not used as a comparative measure to define the treatment response in the meta-analysis due to the studies having a varied method of reporting, with some reporting the percentage of improvement from baseline and others the actual reduction in the score (21).

The long-term studies 303 and 305 were not included due to the study design as they were open label extensions of earlier short-term trials. Studies 303 and 305 were included in EPAR (3) as supportive studies (Table 1). Study 312 was unpublished at the time of the systematic review, however the results were evaluated from the clinical trial results (21).

Extended-release guanfacine was used in all the studies except for the oldest study (Scahill et al, 2001)(50) which tested immediate release guanfacine. The studies were all multi-centre except Scahill et al (2001)(50) which was a single centre study and which was also the only study which was not funded by Shire. The seven studies covered a period from 2001 – 2013. The studies were all defined as randomised in design, however, studies 301, 314, 304 and Scahill et al (2001)(50) did not provide enough information about the randomisation process and only studies 301 and 304 stated that the allocation of guanfacine and placebo was concealed. Study 307 did not disclose how missing data was managed. The inclusion criteria to define the severity of ADHD diagnosis required to qualify as a test subject varied between the studies and the inclusion of co-morbidities also varied between the studies, with study 307 including children with ODD and Scahill et al, (2001)(50) included tics as a co-morbidity. Eleven different outcome measures were used to assess efficacy across the seven studies (21).
Table 1: Details of the efficacy studies included in the EPAR for Intuniv (3) and the systematic review (Ruggiero, 21). Table adapted from results presented in EPAR (3).

<table>
<thead>
<tr>
<th>SPD03 Trial ID/Year</th>
<th>Trial design</th>
<th>Study objective</th>
<th>No. of subjects/ Age/ No. of study centres/ location</th>
<th>Duration</th>
<th>Primary endpoint/ secondary endpoint</th>
<th>EPAR (3)</th>
<th>Ruggiero et al (2014) (21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>304/2004</td>
<td>R, DB, PG, PC</td>
<td>Efficacy; dose- response study</td>
<td>n=322/ 5-17 yrs/51/US</td>
<td>3 wk titrat, 2 wk maint, 3 wk taper</td>
<td>ADHD-RS-IV/ CGI-I, CPRS-R, PGA</td>
<td>primary study</td>
<td>included</td>
</tr>
<tr>
<td>312/2001-2013</td>
<td>R, DB, PG, PC</td>
<td>Efficacy, flexible dose study</td>
<td>n=213/13-17 yrs/52/US</td>
<td>7 week opt, 6 wk maint, 2 wk taper</td>
<td>ADHD-RS-IV/ CPRS-R, CGI-I</td>
<td>primary study</td>
<td>included</td>
</tr>
<tr>
<td>315/2010-2013</td>
<td>RW, DB, PG, PC</td>
<td>Maintenance of efficacy. Randomised withdrawal study.</td>
<td>n=409/6-17 yrs/58/US, Canada, EU</td>
<td>13 wk open, 26 wk R with 2 wk taper</td>
<td>ADHD-RS-IV/ WFIRS-P, CGI-I</td>
<td>primary study</td>
<td>Not included</td>
</tr>
<tr>
<td>316/2011-2013</td>
<td>R, DB, PG, PAC</td>
<td>Efficacy. Flexible dose study.</td>
<td>n=337/6-17 yrs/58/US, Canada, EU</td>
<td>4-7 wk opt, 6 wk maint, 2 wk taper</td>
<td>ADHD-RS-IV/ WFIRS-P</td>
<td>primary study</td>
<td>Not included</td>
</tr>
<tr>
<td>206/2005</td>
<td>R, DB, PC</td>
<td>Dose optimisation study, assess effect on cognitive function. Safety, tolerability, efficacy.</td>
<td>n=182/6-17 yrs/US</td>
<td>6.5 wks,</td>
<td>ADHD-RS-IV/, CGI-I, CANTAB, CRT, DSST/Coding, SWM, PERMP, PSS</td>
<td>Supportive study</td>
<td>included</td>
</tr>
<tr>
<td>313/2009</td>
<td>R, DB, PC, MC</td>
<td>Dose optimisation study. Safety and Efficacy. Combination with Psychostimulant</td>
<td>n=455/6-17 yrs/59/US</td>
<td>9 wk.</td>
<td>ADHD-RS- IV/CGI-I, CGI-S</td>
<td>Supportive study</td>
<td>Not included</td>
</tr>
<tr>
<td>314/2009-2010</td>
<td>R, DB, MC, PC</td>
<td>Tolerability, efficacy. Am and pm dose. Dose optimisation study.</td>
<td>n=333/6-12 yrs/47/US, Canada.</td>
<td>8 wk: 5 wk opt, 3 wk maint, 9 days taper</td>
<td>ADHD-RS- IV/CGI-I</td>
<td>Supportive study</td>
<td>included</td>
</tr>
<tr>
<td>303/2003-2005</td>
<td>long-term open label extension study</td>
<td>To assess long-term efficacy (extension of study 301)</td>
<td>n=240/6-17 yrs/45/US</td>
<td>24 months.</td>
<td>ADHD-RS-IV</td>
<td>Supportive study</td>
<td>Not included</td>
</tr>
<tr>
<td>305/2004-2006</td>
<td>long-term open label extension study</td>
<td>To assess long-term efficacy (extension of study 304 and 205)</td>
<td>n=262/6-17 yrs/48/US</td>
<td>24 months.</td>
<td>ADHD-RS- IV/CGI-I, PGA, CHQ-PFP30, CPRS-R</td>
<td>Supportive study</td>
<td>Not included</td>
</tr>
<tr>
<td>Schiell et al, 2001 (50)</td>
<td>R, DB, PC</td>
<td>Efficacy, Safety study. ADHD patients with tics.</td>
<td>n=34/7-14 yrs/single study centre/US</td>
<td>8 wks</td>
<td>ADHD-RS/CGI-I, CPRS-R, CTROS-R</td>
<td>Not included</td>
<td>included</td>
</tr>
</tbody>
</table>

R = Randomised, PG = Parallel group, PC = Placebo controlled, RW = Randomised withdrawal, DB = double blind, PAC = Placebo and Active Controlled, MC = multi-centre, titrat = dose titration, maint. = maintenance dose, wk = week, yrs = years, opt = dose optimisation, AE= adverse events, taper = dose tapering
4.2 Safety of guanfacine at time of authorisation in Europe

4.2.1 European public assessment report (EPAR) for Intuniv, safety concerns

In the EMA assessment of safety, the results were based on a study population of 2,411, of which 1,718 were aged 6-12 years and 693 were adolescents aged 13 – 17 years, for which the mean exposure time was 142 days (3).

The adverse events for guanfacine were considered typical for alpha2 adrenergic medication, with somnolence, orthostatic hypotension, headache and fatigue commonly occurring. Guanfacine had a potential rebound effect of hypertension and tachycardia upon abrupt termination of treatment (3).

The most common side-effects reported in the studies were somnolence (ca. 40%), headache (ca. 27%), fatigue (ca. 18.1 %) which was dose-related and sedation (ca. 10 %); with there being no significant differences between the different age groups (3). Syncope occurred with 16 of the guanfacine-treated patients (0.7%) and circa 6% of the patients experienced hypotension (3). EMA recommended in their report that pre-treatment screening of patients for medical history of hypotension or conditions that may increase their risk for syncope is necessary and regular blood pressure and heart rate checks should be conducted (3).

Adverse events that were rated as severe nervous system disorders were observed in 4.6% of guanfacine patients (placebo 0.5% and atomoxetine 0.0%), these were severe somnolence (2.7%) and severe psychiatric disorders (1.4%) (3). Sedation and somnolence was considered to be of concern and further investigation and controls post-authorisation were deemed necessary, especially regarding cognitive impairment and neurocognitive development in the child and adolescent patients (3). Psychiatric adverse events occurred in 21.7 % of patients treated with guanfacine, with irritability, mood changes, aggression, depression and suicidal thoughts amongst the symptoms (3).

Cardiovascular effects were considered to be of importance as guanfacine affects heart rate, with a risk of developing arrhythmia. The assessment report recommended that careful medical assessment is undertaken to ascertain which risks a patient has, including full personal and family medical cardiovascular history (3).

Obesity and increased BMI were risks which were identified with guanfacine treatment and in order to minimise the risks, pre-treatment and annual checks on cholesterol, glucose and triglyceride levels were advised for the ADHD patients (3).

EMA noted that there was a potential risk for abuse as guanfacine has a hypno-sedative effect and ADHD is associated with a higher risk of substance abuse. However, there were no clinical trials to assess the abuse risk potential for guanfacine (3).

4.2.2 Treatment discontinuation

Overall, according to the EPAR, guanfacine had the highest rate of adverse events compared to placebo and atomoxetine, especially regarding serious adverse effects (8.8 % for guanfacine, compared with 1.8% for atomoxetine and 1.7 % for placebo). It was noted that approximately twice the number of guanfacine-treated patients (10.8%) discontinued their treatment due to side-effects as compared with the atomoxetine-treated patients (4.5 %) in the study which had atomoxetine as an active comparator and circa an eight-fold increase compared with placebo (1.3%)(3).
4.2.3 Safety reported in systematic review by Ruggiero et al (2014)(21)

Adverse events were reported for all the seven studies, however in the study by Scahill et al (2001)(50) there was a lack of information regarding how the side-effects were distributed amongst the patients, however the actual side-effects reported coincided with those reported in the other studies (21).

4.2.4 Risk-benefit

EMA reported in the EPAR that the risk-benefit ratio was positive for guanfacine due to the efficacy of improving ADHD symptoms providing that recommended risk prevention measures were undertaken. EMA stated that a beneficial effect on functioning was not consistently shown across the studies, however this was acknowledged to be a difficult outcome to measure. However, on 23rd July 2015 there was a divergent position stated by Pierre Demolis, a member of the EMA’s Committee for Medicinal Products for Human Use (CHMP) stating that he considered the benefit-risk balance to be negative due to the inconsistency and low effect on ADHD symptoms together with an inconclusive effect on functioning (3). Pierre Demolis also stated that there were long-term treatment safety concerns and safety risks associated with guanfacine treatment.

Ruggiero et al (2014)(21) also reported a positive risk-benefit ratio, however it was noted that guanfacine was only compared to placebo and there was no information on the non-pharmacological treatment and support the patients were receiving, which is an important aspect of ADHD treatment. It was also noted that there were no randomised long-term studies (21).

4.2.1 Safety update post-authorisation

There have been updates published by EMA since authorisation of Guanfacine, a summary of the steps taken post-authorisation appear in Procedural steps and scientific information after authorisation for Intuniv (44).

On 12th December 2016 an additional warning was added to the Summary of Product characteristics (SmPC) concerning the risk of developing hypertensive encephalopathy following abrupt termination of treatment. Updated drug interaction, pharmacodynamics and metabolism information was added following the completion of requested studies (44).
4.3 Long-term studies

Table 2: Details of the long-term efficacy and safety studies included in the EPAR for Intuniv (3)

<table>
<thead>
<tr>
<th>Trial ID/Year</th>
<th>Trial design</th>
<th>Study objective</th>
<th>No. of children/Age range/No. of study centres/location</th>
<th>Duration</th>
<th>Primary endpoint/Secondary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>303/2003-2005</td>
<td>long-term open label extension study</td>
<td>To assess long-term efficacy (extension of study 301)</td>
<td>n=240/6-17 yrs/45/USA</td>
<td>24 months</td>
<td>Clinical laboratory tests, AE/ADHD-RS-IV</td>
</tr>
<tr>
<td>305/2004-2006</td>
<td>long-term open label extension study</td>
<td>To assess long-term efficacy (extension of study 304 and 205)</td>
<td>n=262/6-17 yrs/48/USA</td>
<td>24 months</td>
<td>Clinical laboratory tests, AE ADHD-RS-IV/CGI-I, PGA, CHQ-PF50, CPRS-R</td>
</tr>
<tr>
<td>318/2013-2015</td>
<td>Long-term open-label extension study</td>
<td>extension study of participants from 315 or 316 in Europe</td>
<td>n=215/6-17 yrs/52/Austria, Belgium, France, Germany, Italy, The Netherlands, Poland, Romania, Spain, Ukraine, UK</td>
<td>24 months: 7 wks opt, 95 wks maint, 2 wks taper</td>
<td>Efficacy: ADHD-RS-IV, CGI-S. Safety: TEAEs, clinical laboratory tests</td>
</tr>
</tbody>
</table>

R = Randomised, PG = Parallel group, PC = Placebo controlled, RW = Randomised withdrawal, DB = double blind, PAC = Placebo and Active Controlled, AE = adverse events, TEAEs = Treatment-emergent adverse events, MC = multi-centre, titrat = dose titration, maint. = maintenance dose, wk = week, yrs = years, opt = dose optimisation, AE= adverse events, taper = dose tapering

Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD (38) (study 303)

Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder (37) (study 305)

Study 303 was a 24-month long-term open-label extension of study 301. The test subjects were screened to ensure that there were no safety issues preventing them from participating. Study 305 was a 24-month long-term open-label extension of studies 304 and 205 (Table 2). Study 205 patients had guanfacine co-administered with psychostimulants, otherwise the other short-term studies contributing to study 303 and 305 had guanfacine in monotherapy (37).

In the EMA assessment report (EPAR) (3), it was noted that there was too limited data in the long-term studies 303 and 305 to be able to assess long-term safety; this being due to the high proportion of test subjects that discontinued the treatment over the course of the study (circa 80 %). According to The International Council for Harmonisation (ICH) Topic E1 on the extent of population exposure to the high recommended-dose required for long-term treatment of non-life threatening conditions, the minimum requirement is one year of treatment for a minimum 100 patients (51). 240 patients were enrolled in study 303, however only 42 completed and out of a total 262 patients in study 305, only 60 patients completed. The most common reason for drop-out was the withdrawal of consent (34 % in study 303 and 28% in study 305) (37, 38).

In study 305, test subjects were considered compliant if they had taken 80 – 120 % of their prescribed amount which was calculated at every check-up, with counting tablets as a control measure (37).
The findings in EPAR for studies 303 and 305 showed that increased BMI was considered a substantial safety risk, with a mean increase of 2.2 BMI points for test subjects that completed the 24 month studies. The cognitive effects of long-term guanfacine treatment were not evaluated, resulting in EMA requesting a long-term phase IV post-authorisation safety study (study ID SPD503-401) to be conducted (final report to be submitted 31st January 2022) with the primary objective to study the cognitive effect of long-term guanfacine treatment and a secondary objective to investigate the risks of adverse events including weight increase, bradycardia, syncope, sedation, and the impact on growth, sexual maturation and QT interval (3).

The overall safety and efficacy findings of the long-term studies 303 and 305, despite the high drop-out rate, were similar to the results of the short-term trials, indicating that the effects of guanfacine are both effective and generally safe both early in the treatment period and are durable over long-term treatment periods. The ADHD-RS-IV scores in study 303 also showed an improvement in ADHD-symptoms for both children aged 6-12 years and adolescents aged 13 – 17 years (38).

### 4.3.1 Long-term study 318 results

Long-term study 318 was conducted in response to satisfy an EU post-authorisation regulatory requirement. The results of this trial which ended late in 2015 are not yet published, however, the clinical results are available for viewing in the EU Clinical register under EudraCT number 2011-004668-31 (40) and are also referred to in an EMA post-authorisation report (39) and in a conference poster presentation (41).

**EU Clinical Trials Register. Clinical Trial Results: Study no. SPD503-318. EudraCT no: 2011-004668-31: A Phase 3, Open-label, Multicentre Study to Provide Access to Guanfacine Hydrochloride Extended-release for European Subjects with Attention-deficit/Hyperactivity Disorder (ADHD) who Participated in Study SPD503-315 or SPD503-316 (40)**

**European public assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) (39)**

**Long-term growth-related safety outcomes of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Poster presentation at the 29th European College of Neuropsychopharmacology (ECNP) Congress; 23-28th September 2016, Vienna, Austria (41).**

Study 318 was an open-label multicentre phase 3 study that gave access to European subjects that had previously taken part in two short-term placebo-controlled studies; 315 and 316. The aim of the study was to evaluate safety and efficacy in long-term guanfacine treatment, with results that are relevant to the European population (39).

The study subjects were from 11 different European countries, conducted over 52 sites, with a total of 215 patients enrolled. Safety outcomes included clinical laboratory assessments, adverse events and physical medical examinations. Efficacy outcome measures were ADHD-RS-IV and CGI-S scales (39, 40) (Table 2).

A total of 133 patients completed the study (62.1%), with withdrawal by the subject the most common reason for drop-out (17.3%), followed by lack of efficacy (8.9%) and then adverse events (3.3%); other reasons included ‘other’ (5.6%), ‘lost to follow-up’ (2.3%) and protocol violation (0.5%) (39).
4.3.1.1 Long-term efficacy, study 318 results

Efficacy was reported to be greater in the adolescent group (aged 13-17 years) compared to the children (aged 6-12 years). 46.4% of patients had achieved a ‘normal/borderline severity’ categorisation of CGI-S at the end of the study, with 63.8% of adolescents and 35.4% of children achieving this result (39, 40).

Regarding ADHD-RS-IV scale ratings, the rating scale measured ADHD symptoms (0-54), with the score of 0 representing no symptoms to 54 representing most severe ADHD symptoms. A mean change in ADHD-RS:IV score from baseline to final assessment of -19.8 was recorded, with the change slightly greater in the 6-12 year old age group (-20.2 mean change) compared to the adolescents aged 13-17 years (-19.3 mean change). At baseline, the mean ADHD-RS-IV rating was higher for 6-12 year olds (40.0 mean rating) than the adolescents (31.2 mean rating) (39, 40).

Lack of efficacy was stated as reason for treatment withdrawal for 14 of the children aged 6-12 years (6.5% of total subjects) and for 5 of the adolescents aged 13-17 years (2.3% of total subjects) (39, 40). Of these total 19 subjects (8.9%) that withdrew from the study due to lack of efficacy, there were individuals included that had some of the most severe ADHD-RS-IV ratings at baseline. Two of the individuals that discontinued the treatment due to lack of efficacy (one from each of the age groups) had co-morbidity ODD. 75.8% (11 individuals) of 6-12 year age group of subjects that withdrew from the treatment due to lack of efficacy had ADHD-RS-IV scores over 38: four individuals with ADHD-RS-IV ratings between 39 – 44; four individuals with ratings between 45-49 and three individuals with ratings >50 (39).

40% (two individuals) of 13-17 year age group of subjects that withdrew from the treatment due to lack of efficacy had ADHD-RS-IV baseline scores over 38 (one individual with a score of 39 and one individual with maximum score 54) (39).

Of these individuals that withdrew, six children and one adolescent had no prior ADHD medication. There were also two children and two adolescents in the group that withdrew due to lack of efficacy that not experienced ≥ 30% reduction in ADHD-RS-IV score from baseline at any of their visits during the trial (39).

4.3.1.2 Long-term safety, study 318 results

An upward shift in BMI had occurred for 12% of the patients, with a shift from normal or overweight BMI at baseline to an increase to overweight or obese at the end of the 95-week study. However, the majority of patients (circa 78%) retained the same BMI category as recorded at baseline (39, 41). 8% of patients decreased their BMI from overweight or normal at baseline to normal or underweight at the final assessment (39, 41).

Adverse events were experienced by 82.7% of the patients, with somnolence, headaches, vomiting, nausea, fatigue, dizziness and insomnia the most frequently reported adverse events. 26.6% of all patients required a dose reduction due to the adverse effects. Reporting of sedation as adverse effect decreased after time, with the mean duration for children 33.6 days and 76.2 days for adolescents. No new safety issues were reported for guanfacine, with the adverse events consistent with previous studies and the drop-out rate due to side-effects was relatively low (38, 40). The benefit-risk ratio was considered to be positive (39).
4.4 Recently published articles since authorisation

An American 8-week, double-blind, randomised control trial from 2016 resulted in two published articles (42, 43) that contributed to further knowledge regarding guanfacine efficacy. The trial was not funded by the drug manufacturer Shire.

*Cognitive Effects of Stimulant, Guanfacine, and Combined Treatment in Child and Adolescent Attention-Deficit/Hyperactivity Disorder* (42).

*Cognitive Effects of Stimulant, Guanfacine, and Combined Treatment in Child and Adolescent Attention-Deficit/Hyperactivity Disorder* (42).

The clinical trial was an 8-week randomised, double-blind comparative trial involving children aged 7-14 years with ADHD. The trial had three arms: patients treated with guanfacine; patients receiving combined treatment with d-methylphenidate extended release and guanfacine; and an arm receiving mono treatment with d-methylphenidate extended release. Although these are newly published articles, they are based on trial NCT00429273 which was completed in 2011. Guanfacine extended release was therefore not available at the time of this trial and guanfacine immediate release was used instead (42).

4.4.1 Results: Cognitive effects of treatment

The study by Bilder *et al* (2016) (42) had 182 child and adolescent patients aged 7 – 14 years old that completed the 8-week trial. The patients had ADHD with a CGI-S rating of ≥ 4 and did not have any co-morbidities or pre-existing medical conditions that were contraindicated for guanfacine or stimulant treatment. A comparison reference group was used, which consisted of 93 children that did not have any history of ADHD or other related psychological disorders. There were three arms of the study: the d-methylphenidate arm was treated with placebo from baseline to midpoint at 4 weeks, then d-methylphenidate extended-release (5-20 mg/day) from week 4 to week 8; the combination arm was treated with guanfacine from baseline to week 4, then with d-methylphenidate and guanfacine (1 – 3 mg/day) in combination from week 4 to 8; the guanfacine arm was treated with guanfacine from baseline to week 8. At week 4 all subjects were considered to be receiving their correct optimal titrated dose (42).

Cognitive assessment tests were conducted at baseline, at week 4 and at week 8 and consisted of tests to assess working memory (6 tests), reaction time (4 tests), inhibition (5 tests) and reaction time variability (5 tests). The test results of the treatment arms were compared to the non-clinical reference group (42).

The most significant treatment results were on the working memory domain which were for the combined treatment or the d-methylphenidate treatment, which were equally high, however there was no change in the guanfacine arm (Table 3). Regarding the inhibition, reaction time and response time variability, these domains showed an improvement at week 8 from baseline, regardless of the treatment (42).

The study concluded that monotherapy with guanfacine does not have positive effects on cognitive outcomes. It also concluded that combination treatment with guanfacine and d-methylphenidate does not improve efficacy on cognitive outcomes when compared to monotherapy with d-methylphenidate. Clinical improvements regarding behavioural outcomes for combination treatment in ADHD patients compared to monotherapy suggests that this improvement does not reflect cognition changes (42).
**4.4.2 Results: Combined Guanfacine and stimulant treatment comparisons**

The second article by McCracken et al (2016)(43) was to assess whether combined therapy with guanfacine and d-methylphenidate would be superior to either guanfacine or d-methylphenidate as monotherapy.

207 children were enrolled onto the 8 week study which had three arms. The first arm had placebo baseline to week 4, then placebo combined with d-methylphenidate week 4 to 8. The second arm had guanfacine from baseline to week 4 and guanfacine plus placebo week 4 to 8. The third arm had guanfacine from baseline to week 4 and guanfacine combined with d-methylphenidate from week 4 to 8 (43). CGI-S and ADHD-RS-IV were used to measure symptoms at baseline and CGI-I was rated at baseline and at the end of every week (43).

The combined treatment with guanfacine and d-methylphenidate had a better outcome on the ADHD-RS-IV total score than the monotherapy with guanfacine (Table 3). However, the combined therapy did not demonstrate a statistically significant improvement compared with the d-methylphenidate in monotherapy (Table 3). Differences in CGI-I treatment response varied however, with 91 % for the combined treatment, 81 % for monotherapy with d-methylphenidate and 69 % for monotherapy with guanfacine (Table 3). The adverse events were mainly mild or modest in severity and did not differ between the different arms of the study (43).

**Table 3.** Summary of results from articles by Bilder et al (2016)(42) and McCracken et al (2016)(43) to compare effects of stimulant, guanfacine and combined stimulant and guanfacine treatment in child and adolescent ADHD patients.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Combined</th>
<th>Monotherapy guanfacine</th>
<th>Monotherapy d-methylphenidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>working memory (42)</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>reaction time (42)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Inhibition (42)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>reaction time variability (42)</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Efficacy: ADHD-RS-IV (43)</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Efficacy: CGI-I % difference (43)</td>
<td>91 %</td>
<td>69 %</td>
<td>81 %</td>
</tr>
</tbody>
</table>

++ = most significant improvement, + = significant improvement,- = no significant change

**4.4.3 Results: Guanfacine efficacy following prior methylphenidate treatment**

A recently published analysis focused on efficacy of guanfacine following prior methylphenidate treatment; the analysis was based upon data from the international phase III Shire trials 316 and 315 (Huss et al, 2016)(31).

**Guanfacine extended release for children and adolescents with attention-deficit/hyperactivity disorder: efficacy following prior methylphenidate treatment (31)**

Study 316 was a double-blind, parallel-group, multicentre placebo-controlled randomised controlled trial (RCT) with children aged 6-12 years and adolescents aged 13 – 17 years. The treatment was randomised at baseline, with one arm receiving guanfacine extended release (GXR), the second arm was a reference arm with atomoxetine (ATX) and the third arm had placebo. The adolescents had a higher dose of GXR at 1–7 mg/day compared to the children who were given 1-4 mg/day. The study duration was also longer for the adolescents at 13 weeks and shorter for the children at 10 weeks (31).
Study 315 was a double-blind, multicentre, placebo-controlled randomised withdrawal study (RWS) with children aged 6-12 years and adolescents aged 13 – 17 years. The study commenced with open-label dose optimisation of guanfacine over the first 7 weeks, followed by dose maintenance for 6 weeks. Thereafter the patients were randomised to either continue the guanfacine treatment or to receive placebo (31).

For all participants of these two studies, prior stimulant use was recorded at baseline by using a questionnaire, including detailed reasons for ceasing the treatment; however, duration of the prior stimulant treatment was not noted (31). The results of the trials were analysed according to the patients’ previous stimulant treatment with the information captured via the questionnaire completed by the participants at baseline. The patients with prior stimulant exposure were categorised as either ‘prior methylphenidate (MPH)’ or ‘prior non-MPH’. The primary outcome measure to assess efficacy was change in ADHD-RS-IV (31). CGI-I and CGI-S scores were also recorded (31).

In study 316 there were 337 participants of which 163 (48.5%) had been treated with stimulants prior to the study. Of these participants, 142 had received methylphenidate and these participants were represented evenly across the three study arms. The remainder of participants that had received ‘non-MPH’ stimulant was a very small group and the medications represented were varied, therefore this group was excluded from the analysis of these results. The remaining ‘stimulant naïve’ patients were approximately half of the remaining study population (n=174, 51.6%) (31).

In study 315 there were 296 patients (58.8%) that had prior stimulant use, of which 224 (44.5%) were last treated with MPH, again, the ‘non-MPH’ group was small and excluded from this analysis. The reported ‘stimulant-naïve’ group in this RWS consisted of 207 participants (41.2%) (31).

The reasons for the patients terminating the previous MPH were collated with a questionnaire. For the RCT study 316, the most common reason stated for discontinuing MPH treatment was the 'lack of effectiveness' (56 %) and in study 315 it was also the most common reason at 65%. ‘Side-effects’ was the next most common reason; (study 316: 37%, study 315: 55%). ‘Wanting to switch medication’ was a reason stated by 29% of study participants in study 316 and ‘wanting to stop taking stimulant medication’ was stated as a reason for 11% of participants in study 315 (31).

In the RCT study 316, there were significant changes in ADHD-RS-IV noted for guanfacine patients that were either ‘stimulant-naïve’ or for those that had prior MPH treatment. The result for atomoxetine demonstrated a smaller change in ADHD-RS-IV in ‘stimulant-naïve’ patients than those with guanfacine, however the group of atomoxetine patients that had prior stimulant exposure did not demonstrate a significant change in ADHD-RS-IV score (31). In RWS study 315, there was only a small difference in ADHD-RS-IV score between prior MPH patients and those that were ‘stimulant-naïve’, with the most change noted in the stimulant-naïve patients (31).

When measuring the outcomes by improvement of CGI-I and CGI-S, the patients that were ‘stimulant naïve’ showed greater improvements to CGI-I and CGI-S, this was demonstrated across the guanfacine arms in both studies and also in the atomoxetine arm; in the placebo control group there was no statistically significant difference between the two categories (31). However for both ATX and GXR, there was no statistically significant result for participants that had prior MPH treatment, regarding CGI-I scores (31).

<table>
<thead>
<tr>
<th>Measure</th>
<th>GXR (MPH-naïve)</th>
<th>GXR (prior MPH)</th>
<th>ATX (MPH-naïve)</th>
<th>ATX (prior MPH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 316: ADHD-RS-IV</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Study 315: ADHD-RS-IV</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Study 316: CGI-I &amp; CGI-S</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Study 315: CGI-I &amp; CGI-S</td>
<td>++</td>
<td>-</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

GXR = guanfacine extended release, MPH = methylphenidate, ATX = atomoxetine, + = small yet significant change, ++ = significant change, - = no significant change, N/A = not applicable

4.5 Comparison of efficacy and safety of guanfacine with other ADHD medications

Due to there not being any head-to-head comparisons with guanfacine and other ADHD medications, two reviews published within the last 12 months have been selected which look at a comparison of efficacy and safety for ADHD medications.

A systematic review funded by Shire written in 2017 by Joseph et al (46): Comparative efficacy and safety of attention-deficit/hyperactivity disorder pharmacotherapies, including guanfacine extended release: a mixed treatment comparison (46).

The systematic review by Joseph et al (2017)(46) was based upon studies of ADHD patients aged 6-17 years; co-morbidities were exempted. The efficacy outcomes which were included in the meta-analysis were ADHD-RS-IV, CGI-I, ‘all-cause discontinuation’ and ‘discontinuation due to adverse events’ (46). The drugs which were included for the analysis were GXR, LDX, ATX and both extended- and immediate-release formulations of MPH. 43 articles were included in the systematic review dated 1994 – 2016.

The outcome of the analysis revealed that the greatest efficacy as measured in ADHD-RS-IV score change from baseline compared with placebo was achieved by LDX (mean change -14.98), MPH immediate release had the second best efficacy (mean change - 9.33), followed by GXR (-8.68) and ATX (-6.88). With regard to the greatest improvement measured in CGI-I, LDX demonstrated the highest relative risk for treatment response when compared with placebo (2.56), followed by MPH extended release (2.13), GXR (1.94), ATX (1.77) and MPH immediate release (1.62) (46).

The risk ratio estimates for the outcome measure ‘all cause discontinuation’ for each drug compared with placebo were highest for ATX (0.88), followed by GXR (0.87), LDX (0.66), MPH extended-release (0.52) and lowest for MPH immediate release (0.44). The risk ratio estimates for the outcome measure ‘discontinuation due to adverse events’ compared with placebo were highest for GXR (4.49), followed by LDX (3.11), ATX (2.39), MPH extended release (1.38) and MPH immediate release (1.20) (46).

A study independent from Shire written by Li et al (2016): Combined Stimulant and Guanfacine Administration in Attention-Deficit/Hyperactivity Disorder: A Controlled, Comparative Study (47).

The study was based on the results of 62 studies, and included medications bupropion and clonidine hydrochloride (both of which not licensed for ADHD treatment in Europe),
GXR, ATX, MPH and LDX. There were different outcome measures represented across the studies, with the efficacy measure for GXR limited to just ADHD-RS-IV (47).

LDX was found to be the most effective medication with regard to the outcome measures ADHD-RS-IV and CPRS (47). Regarding safety, bupropion had the highest probability of ‘all-cause withdrawals’ and when comparing ‘all-cause’ withdrawals to placebo; bupropion, MPH and LDX all had significantly higher incident rates (47). GXR and ATX had the lowest probability of withdrawal, however, amongst the patients that reported withdrawal due to adverse events, incidence of severe adverse events was highest for GXR (47). MPH had the lowest incidence of causing adverse effects and subsequent treatment drop-outs due to side-effects (47). MPH was estimated to be the second most efficient ADHD medication after LDX when measured with ADHD-RS-IV and third most efficient after LDX and clonidine when using the CPRS measurement (47).

4.6 Role of Parents in decisions regarding child ADHD medication

Three original articles were selected which explored parental decisions regarding their child’s ADHD pharmacotherapy.

The first study was based in USA and written by Cormier (2012)(19): *How parents make decisions to use medication to treat their child's ADHD: a grounded theory study* (19).

16 semi-structured interviews of parents aged 31-48 years (13 mothers, 3 fathers) of children (aged 6-12 years with ADHD and currently receiving ADHD medication) were undertaken to understand the reasoning behind the decisions regarding their child's ADHD pharmacotherapy. The interview sessions were conducted face-to-face with every parent and each lasted 60-90 minutes and were spread over a period of 10 months. The semi-structured interviews commenced by the interviewer choosing initial open questions from a list and then asking subsequent questions to encourage the interviewee to elaborate more on their previous answers. The interviews were all digitally recorded and transcribed. There were 16 children represented, 8 of these had ADHD with co-morbidity and the ADHD medication was varied, with both stimulant and non-stimulant medications represented (19).

The interview transcripts were then ‘coded’ to theme the responses according to the interpreted meaning behind the statements. The substantive theory identified was a process of the parents ‘doing what helps most’ when making decisions about their child’s ADHD medication. Six stages were identified during this process; the first being resisting starting ADHD medication and then followed by a second stage of struggling to receive help. The third stage is releasing control of the situation as coping with the child’s problems becomes too difficult. The fourth stage is positive appreciation of the changes brought on due to their child’s ADHD medication and the fifth stage is managing the adverse effects and issues surrounding the administering of the ADHD treatment (19). The sixth stage is parents’ acceptance of the treatment, however this is accompanied by doubts and worry combined with the need to manage the adverse effects of the ADHD medication (19).

The child’s ADHD symptoms were described as disrupting family harmony, causing stress and exhaustion (19). The stress and exhaustion experienced by the parents was challenging during the time when important decisions regarding ADHD medication needed to be made (19).

The first stage of resisting treatment was reported to have been subject to influences related to a negative stigma, worrying about side-effects, also believing that their child
may mature and outgrow the symptoms. Also, many parents reported that they felt that they were responsible for helping their child and did not want their child to instead be helped by medicines. The lack of understanding of ADHD diagnosis and conflicting opinions and negative attitudes from others coupled with the negative stigma of giving their child stimulant medication led to resisting ADHD medication (19). There was also a fear of the effects of stimulants on their child (19). However, once the decision had been made to commence ADHD medication the parents reported positive outcomes, with improvements in family life with reduced stress and disruption and improvements at school. The fifth stage of managing side-effects was also characterised by worry about long-term effects of ADHD medication on their developing child (19).

The second study was also based in USA and was written by Coletti et al (2012) (48):

*Perspectives on the Decision to Initiate Medication Treatment of Attention-Deficit/Hyperactivity Disorder (48).*

The study design was five focus groups consisting of a total of 27 parents (78% women) to 5-12 year old children with ADHD who had received a recommendation to begin stimulant ADHD treatment. Approximately one third of the children had a co-morbidity. Approximately 81% of the parents had followed the recommendation for their child to start medication, however every focus group included parents that had resisted starting stimulant medication or had discontinued the treatment (48).

There were three themes identified from the focus groups: ‘defining adherence’, ‘attitudes that promote or interfere with adherence’ and ‘parent perceptions of medical providers’ (48). There were varying definitions of treatment adherence amongst the parents and it was evident that the parents administered the medication in varied ways, with different timings, varied dosing and varying administration methods. The positive attitudes that promoted adherence included the belief that the medication was effective in reducing ADHD symptoms and that it promoted improvements in academic ability and social functioning and also that it kept their child safe (48). The negative attitudes included fears about adverse effects and the safety of the medication. Another attitude amongst parents that was noted was to deter the recommended treatment whilst instead trialling non-pharmacological behaviour modification and training (48).

The parents’ perception of the medical providers at the time of the medication recommendation were both negative and positive. The positive elements were a collaborative approach to the treatment decision and also taking the time to explain the treatment and diagnosis. It was however discussed that the parents felt that it was important for the medical provider to realise that it is fundamentally the parents themselves who make the decision for their child to start stimulant treatment (48). The parents also reported that the balance of the level of the complexity and amount of detail of the information given to them by the medical provider was important (48).

Negative emotional responses were noted from the parents including self-blame for their child’s condition and fear about their child’s medication. Issues with self-image were also discussed amongst the parents, due to negative responses received from their social circles when their child’s stimulant treatment was disclosed. Social pressures were also reported to cause the parents to be secretive about their child’s medication. Social pressures from family members and spouses recommending alternative child rearing behavioural methods were also noted (48).

It was noted that parents need to be given clear information about how the medicine should be administered to their child and also adherence needs to be followed up regularly (48).
The third study was based in Australia and written this year by Ahmed et al (2017) (49):

*Parents’ Perspectives about Factors Influencing Adherence to Pharmacotherapy for ADHD* (49).

Three focus groups consisting of 16 parents (9 male, 7 female) had discussions about factors which affect the initiation, continuation or discontinuation of their child’s ADHD medication. The children were aged 3–12 years and all had current ADHD medication or had received ADHD medication within the last 6 months. The ADHD medicines were methylphenidate, dexamphetamine or atomoxetine. Each of the focus groups had a duration of 1–1.5 hours and were each facilitated by a researcher. The discussions were recorded and transcribed (49).

There were five themes identified by the researchers which were considered to influence the parents’ decision-making with regard to their child’s medication: ‘parental motivators to commence pharmacotherapy’, ‘observed benefits of pharmacotherapy’, ‘parental experiences with side effects’, ‘parental opinions about long-term effects of pharmacotherapy’ and ‘parental experiences of stigma’ (49).

An important motivator to start ADHD medication noted by the parents was the concern over their child’s failing academic performance (49). A positive influence for continuing ADHD medication is positive changes in the child’s behaviour and even associated improvements in performance at school and social functioning (49). However, many of the parents were reported to have an expectation that the ADHD medication was limited to short-term use (49).

‘Parental experiences with side effects’ was noted to be a major factor that resulted in discontinuation of ADHD treatment and also led to parental modification of the treatment by lowering their child’s dose (49). Concerns and fears of long-term treatment leading to abuse and addiction, particularly in adolescents were also noted and led to treatment discontinuation. Parents also experienced social stigma due to their decision to medicate their child, this was from both family members, parents of other children at school and the general public, resulting in isolation, lack of support and frustration (49).

5. Discussion

5.1 Discussion: method

The search method used produced a large number of search results due to removing search filters in order to ensure relevant articles were not omitted. The time taken to search may have been reduced by selecting a more specific choice of search keywords, resulting in less articles to read through and select. However, the resulting wide range and large number of search results gave a rich source of information to draw upon in order to be able to present a current status of knowledge regarding the safety and efficacy of guanfacine. A more systematic approach to selecting the articles would have strengthened the review as selection would have been less prone to possible bias.

5.2 Efficacy

An important aspect to consider when analysing ADHD treatments is that the treatment outcomes specified in the studies are measured by clinicians and parents, regardless of the age of the patients. This leads to a complex situation as the results are based upon subjective ratings and the child’s experience of the treatment is not mentioned or
assessed in these studies. This leads it to being problematic to be able to truly measure efficacy by using indirect subjective rating scales and also the non-pharmacological interventions which affect the children or adolescent vary for each person and also over a period of time.

It is common for there to be co-existing psychiatric disorders with ADHD and these include: conduct disorders, autism spectrum disorder, oppositional defiant disorder, anxiety/mood disorders, major depression, obsessive-compulsive disorder, bipolar disorder and addictive disorders (52). Co-morbidities are often an exclusion criteria for the ADHD subjects in clinical trials, however since psychological co-morbidities are common in the ADHD population this would seem to suggest that these trials are not representative of the patients taking ADHD medication. This may indeed have a bearing on the individual responses to ADHD medication as co-morbidities can develop over time and also the changing of the presentation of ADHD over time contributes to changes in treatment response.

ADHD treatments need to address ADHD symptoms, the cognitive deficits and the social aspects, which suggest a requirement for carefully balanced treatment programmes with both pharmacological and non-pharmacological aspects, with regular assessments. The mechanisms behind ADHD are not exactly known, and these appear to have individual variations which indeed change over time. The outcome measurements in studies appear to be limited as they are subject to bias due to the parents having a role in assessment and this in turn is due to the lack of biological markers to diagnose ADHD. The existing rating scales would however be more effective if there were an international standard established which specified how they are used in studies.

Considering that ADHD may have a genetic link (6), it is also important to realise that the parents and even siblings of the child may possibly have ADHD and this may affect how these parents are able to assess the ADHD symptoms in their children by filling out questionnaires or indeed being able to remember all the details for example. It would also present a problem in helping to manage a child’s medicine regime and to ensure adherence to this. Indeed the parent’s lack of satisfaction with the effect of ADHD medicine on their child may be a reflection of perceived lack of help they have, which can be influenced by their own needs for support, particularly if they themselves have undiagnosed ADHD.

5.2.1 ADHD symptoms

Guanfacine was considered as effective in improving ADHD symptoms. The pivotal studies in the EMA report (3) all had ADHD-RS-IV symptom rating scale as the primary endpoint to measure outcomes, however studies 312, 315 and 316 had a secondary endpoint, WFIRS-P, to measure global functioning which is required for ADHD studies as effect on social functioning in ADHD treatment is an important area to address and not solely ADHD symptoms (3). Due to the lack of standard use of the rating tools for assessing efficacy, and also the inherent risk for subjective bias, the task of pooling in data from different studies is difficult. The effect size 0.7 of the guanfacine arm in study 316 was higher than the atomoxetine arm effect size of 0.3; however, this was also the study which had the highest drop-out rate in the pivotal studies in EPAR, 52% in the two active arms guanfacine and atomoxetine compared with 67% in the placebo arm (3). The highest proportion of the drop-outs occurred in the guanfacine active arm which was 30% of the 52% drop-out rate due to treatment failure and atomoxetine arm 22 % of the 52% drop-out rate (3). This may suggest that guanfacine is less effective due to the high rate of treatment failure, despite the higher effect size.
5.2.2 Functioning

The EPAR for Intuniv reported that Intuniv had a positive effect on ADHD symptoms as measured by ADHD-RS-IV, however the results on improvements in functioning were lower (3). The outcome for functioning was measured with the rating scale WFIRS in three of the studies (312, 315 and 316), however improvements were only noted in study 316. The EMA stated that there was an uncertainty to the benefits of Intuniv due to the lack of effect on functioning, which is an important aspect of ADHD treatment; however, the reduction of ADHD symptoms is an important aspect and Intuniv demonstrated efficacy superior to placebo at reducing ADHD symptoms (3). EMA concluded that the benefit-risk balance for Intuniv was positive for guanfacine use in individuals with ADHD aged 6-17 years for whom stimulant medication had been unsuccessful or was not appropriate; provided that risk prevention recommendations were undertaken (3).

5.2.3 Cognitive effect

Cognitive outcomes appeared not to be improved by guanfacine treatment, however Bilder et al (2016)(42) propose that this may be due to the combination of an increased sedative effect (with a negative effect on cognition) and a positive increase in cognition due to guanfacine treatment (42). In the earlier study 206 which studied the cognitive effects of guanfacine on cognition, it was also noted that the sedative adverse events of guanfacine may reduce the cognitive ability in patients, however the study concluded that guanfacine could also indirectly improve cognitive ability by reducing ADHD symptoms which in turn influenced the potential to perform better at cognitive tasks (3). It was also noted by Bilder et al (2016)(42) that guanfacine treatment did not result in a negative impact on cognitive ability despite the common adverse events of sedation, fatigue and somnolence (42). The measures to assess cognitive function in the studies appeared to be subject to bias, also the complexity of measuring cognitive function requires possibly more sophisticated comprehensive tools, since the selection of multiple tests varies and leads to results that are difficult to compare.

It was noted by McCracken et al (2016)(43) that the patients’ doses were optimised according to clinical response and not according to levels of cognitive improvement. It would be interesting to conduct a study to evaluate whether cognitive improvement is actually dose related and, if guanfacine was dose optimised according to best cognitive response, how this would affect ADHD-RS-IV scores, adverse events and safety profile of guanfacine treatment.

There was not an increase in reported adverse events in the combined d-methylphenidate and guanfacine treatment group; and the positive impact on CGI-I was greater in this combined treatment arm than with mono-treatment of either of the medications in the other two study arms (43). The studies by Bilder et al (2016, 42) and McCracken et al (2016)(43) were however based upon trial data from 2011 and extended release guanfacine was not available then, so it is questionable how relevant these findings are for today’s ADHD patients that are prescribed extended-release guanfacine.

5.2.4 Effect of prior stimulant treatment on guanfacine efficacy

Guanfacine is indicated to treat individuals that have experienced a suboptimal treatment response to stimulants, including intolerance to stimulants; therefore, the effect of prior stimulant treatment on guanfacine efficacy is a clinically relevant area to explore.

According to Huss et al (2016)(31), the results in their analysis showed a similar effect of
guanfacine in patients that have had prior MPH treatment compared to stimulant-naïve patients; however, the patients with prior stimulant exposure receiving ATX did not demonstrate a significant change in ADHD-RS-IV score. This was considered to be a clinically relevant finding due to the indication of guanfacine in Europe, which states that guanfacine is for use in ADHD patients that have had an unsatisfactory response to stimulant therapy or for whom stimulant therapy is unsuitable (31). Huss et al (31) theorise that this may be due to the difference in mechanisms of MPH and GXR as the results in patients that had prior MPH treatment and were subsequently treated with ATX demonstrated a lower response, which may be due to a similarity in MPH and ATX mechanisms of action (31).

It is interesting to take into account the reasons behind why patients discontinue their MPH treatment. It may be assumed that this is due to the stimulant treatment not suiting the patient, or as Huss et al (31) reported, reasons stated by the test participants included 'wanting to switch medications' and also 'wanting to stop taking stimulant medication'. To be able to best predict which treatment would suit a patient it may be, as Huss et al (2016)(31) stated, that current research suggests that genetic biomarkers may determine response to ADHD medications; however, not all reasons for stopping MPH treatment were due to ineffectiveness or side-effects, but due to personal choice, including safety concerns. An in-depth consultation with parents before their child starts ADHD pharmacotherapy could therefore help screen out preferences and even aid to increase understanding of the medications and to discuss the risks.

5.2.5 Long-term efficacy

Guanfacine demonstrated good safety and efficacy over a 24-month period, satisfying post-authorization requirements by EMA (39). However, there was a greater efficacy reported in the adolescent group (aged 13-17 years) compared to the children (6-12 years), with 63.8% of adolescents and 35.4% of children achieving the CGI-S category of 'normal/borderline' severity at the end of the trial (39). There were however differences in the level of ADHD symptom severity shown at baseline, with a lower mean ADHD-RS-IV rating score for the adolescent group (31.2) than the younger group (40.0). This may suggest that the group with less ADHD symptom severity achieved greater efficacy with the guanfacine treatment.

There were 19 test subjects that withdrew from treatment due to lack of efficacy; 14 children aged 6-12 years (6.5% of total subjects) and 5 adolescents (2.3% of total subjects) (39). These individuals that withdrew had severe ADHD-RS-IV ratings at baseline (indicating severe ADHD symptoms), some had no prior ADHD medication and some had not experienced ≥ 30% reduction in ADHD-RS-IV score from baseline at any of their visits during the trial; two individuals had co-morbid ODD. (39). There were a greater number of child subjects compared to adolescent subjects that withdrew that had higher ADHD-RS-IV scores; seven children had ADHD-RS-IV scores between 45-54 (scale is rated 0-54), and one adolescent had the maximum score of 54 (39). This would suggest that there is possibly a link between lack of efficacy with guanfacine treatment in individuals that have more severe ADHD symptoms or that have co-morbidity ODD; and, as the children (aged 6-12 years) had generally higher ADHD-RS-IV scores than the adolescents, this may explain why the children experienced less efficacy. This is in contrast to the earlier studies which reported less efficacy for adolescents, however this was explained as possibly due to too low dose (3).

5.3 Safety

Guanfacine was considered to be safe, with mild adverse effects, providing recommended risk prevention measures are undertaken (3); side-effects include sedation, hypotension,
bradycardia and nausea. Other risks identified were obesity and increased BMI, this is in stark contrast to side-effects of stimulants or atomoxetine which have a negative effect on growth and weight. An adverse effect of concern for guanfacine is a rebound effect due to abrupt termination of treatment which causes hypertension and tachycardia, this is an important issue due to the problems experienced by patients to adhere to their medication over long-term treatments.

5.3.1 Long-term safety

Long-term use of guanfacine over a 24-month period was considered as safe and effective, however as the long-term studies were over a 24-month period these do not reflect the use in the ADHD patient population where medication can be taken for even more than five years, thus a need for long-term studies over a longer period are required (9). Sallee et al (2009)(37), the limitations of the open-label study design of the long-term study were acknowledged however it was also noted that due to ethical considerations it would be problematic to conduct a blinded placebo-controlled long-term study (37).

The post-authorisation study 318 was also an open-label study over a 24-month period and also had a high drop-out rate (62.1%); however, with a total of 133 patients completing the study, this would be considered to meet the minimum of 100 patients as specified by The International Council for Harmonisation (ICH) Topic E1, unlike the previous two long-term open-label studies reported in Sallee et al (2009)(37) and Biederman et al, 2008)(38).

The proportion of patients that experienced adverse effects in study 318 was high (82.7%) (39). However, the sedative adverse effects (which are also of concern when considering the effect on cognitive performance), were mainly observed during the first weeks of treatment (39). An upward shift in BMI was observed in 12% of the patients, however the majority (78%) maintained their BMI category throughout the study (39). There were no new safety issues identified and the risk-benefit was considered to be positive. Again, this is based on an open-label study which is sponsored by Shire, this and the lack of published material for this trial results in a biased limited view, however, the findings have appeared to satisfy the post-authorisation requirements of EMA (39).

The aim of ADHD pharmacotherapy is to reduce symptoms, yet is not a cure, resulting in long-term treatments. The ongoing safety and efficacy of ADHD medicines over long-term treatment is therefore important. A complication in assessing efficacy of long-term medication is the changing presentation of ADHD which manifests as a decline in ADHD symptoms as the individuals grow older (9). Another factor which complicates assessing long-term ADHD pharmacotherapy is the changing external environment and changing social pressures that the children face as they grow older, also varying levels of adherence over time affect evaluation of the therapy (9).

5.4 Comparison of ADHD medications

There is a lack of direct head-to-head comparative studies looking at the differences in safety and efficacy in the different ADHD medications. Using two reviews which estimated the comparative effects by pooling data from different studies and then subsequently selecting parts of the reviews that were interesting for this review resulted in information that is not necessarily accurate or representative, however it provided information on the current understanding in this area.
In the systematic review by Joseph et al (2017)(46), guanfacine had greater efficacy than atomoxetine according to change in ADHD-RS-IV score from baseline compared with placebo and also when measured with CGI-I. However, greater efficacy was shown by the stimulant medications LDX and MDH. A negative result for GXR was estimated to have the greatest probability for ‘discontinuation due to adverse events’ and had a similar risk ratio to atomoxetine (which scored highest) in the outcome measure ‘all cause discontinuation’ (46). These results seem to suggest that the stimulant medications were superior to guanfacine in their efficacy and adverse event profiles (46). The EPAR (2015)(3) also reported a higher incidence of treatment discontinuation due to adverse events for guanfacine than atomoxetine (3). In study 316 guanfacine had a high drop-out rate which was primarily attributed to treatment failure (3). It was not stated in the systematic review Joseph et al (2017)(46), which reasons were included in the outcome measure ‘all cause discontinuation’, however this may too have been due to insufficient response.

In the comparative study by Li et al (2016)(47), it was also concluded that the greatest efficacy was shown for LDX, which concurs with the review by Joseph et al (2017)(46). However, in the study by Li et al (2016)(47), GXR was considered to have a low probability for treatment withdrawal, but had the highest rate of severe adverse effects (47).

5.5 Parental role in ADHD treatment decision-making

Parents of children with ADHD are involved in the treatment decisions regarding their children’s ADHD. Understanding the decision-making processes and the influences on the parents can contribute to the pharmacist’s counselling role, giving support at a difficult time.

5.5.1 Study design

In the study by Cormier (2012)(19), which involved semi-structured individual parent interviews, it was concluded that parents were involved in a ‘doing what helps most’ process when trying to find and give help to their children. The six stages of the process of ‘doing what helps most’ were interesting as they explain how the decision-making process relating to their child’s ADHD medication evolves over time (19). As a pharmacist, trying to identify which stage the parent is in is essential in order to be able to support and guide them through this process, which is a challenging journey and is of importance not only to the child, but also to harmony at home and at the school, affecting the quality of life for many.

The structure of the Cormier study (2012)(19) which consisted of individual semi-structured interviews seemed to be a good design as the focus group designs in the other two studies Coletti et al (2012)(48) and Ahmed et al (2017)(49) may have been affected by the individuals not wanting to mention certain aspects when in a group setting, or that the group’s discussions influence the input of the individuals. There were also predominantly female parents in the Coletti et al (2012) and Cormier (2012)(19) studies. There was also a risk for lack of objectivity as in the Cormier study (2012)(19) and Ahmed et al (2017)(49) interviews and focus groups were conducted by the researchers, however, in the study by Coletti et al (2012)(48) the focus groups were conducted by child psychologists. In all three studies, the sample size was small, with only 16 parents in both Coletti et al (2012)(48) and Cormier (2012)(19) and 27 parents in the study by Coletti et al (2012)(48). The small sample size, although practical to conduct interviews and focus groups may be too small to be representative.
An interesting factor in the Ahmed (2017)(49) focus group study which was based in Australia is that the children were aged 3-12 years, which is younger than the children which are represented in the studies in this literature study. ADHD is treated according to different guidelines all over the world, in Australia the population age for ADHD treatment for children and adolescents is 2-12 years (children) and 13-18 years (adolescents) (53).

### 5.5.2 Parental concerns

Fear of medication and concerns about the negative social stigma surrounding ADHD stimulant treatment were noted by the parents in the studies by Cormier (2012)(19), Coletti et al (2012)(48) and Ahmed et al (2017)(49). In the study by Coletti et al (2012)(48) there were three themes identified by the focus groups: ‘defining adherence’, ‘attitudes that promote or interfere with adherence’ and ‘parent perceptions of medical providers’. An issue that was raised by the parents was the importance of medical providers to have a collaborative role in decisions regarding their child’s medication, which seemed to reflect the desire for the parents to feel that their authority of making the final decision regarding stimulant medication for their child to be acknowledged. This is an important fact to consider as a pharmacist when giving advice (48). Coletti et al (2012)(48) also stated that it was important to think about how the information is given, with appropriate complexity yet nonetheless comprehensible to the parent.

There were issues raised that highlighted that there was a lack of understanding as to how to administer the medicine and varying levels of adherence and even in defining adherence (48). This raised the importance of providing adequate information about the medicines and also highlighted an important role for a pharmacist to regularly check adherence with the parents (48).

In the study by Ahmed et al (2017) there were five themes identified; ‘parental motivators to commence pharmacotherapy’, ‘observed benefits of pharmacotherapy’, ‘parental experiences with side effects’, ‘parental opinions about long-term effects of pharmacotherapy’ and ‘parental experiences of stigma’ (49). Fear of their child’s academic failure at school appeared to motivate the parents to initiate their child’s ADHD pharmacotherapy. However, the parental experience of the side-effects, including the fear of anticipated side-effects, was a strong factor behind parental decision to either modify or to discontinue their child’s treatment. The focus groups were all parents of children with no parents of adolescents represented. However, the parents expressed fears that their children, once adolescents would be at risk for developing an addiction if they continued the ADHD treatment (49). This is worrying that parents would decide to cease ADHD treatment at an age where there is increased social and academic pressures on the adolescents; this may be important to consider when counselling parents of children that are approaching teenage years.
5.5.3 Parental needs

However, despite the studies having different designs, different geographical studies and that two of the studies were written five years ago and one written this year, the findings were similar. The similarity in the findings may indicate that that parents are still in great need of support when making decisions which affect the management of their child’s ADHD medication and that this is a matter of perhaps global concern. Pharmacists have an important role in the community giving help and guidance to parents, in order to optimise adherence and to address concerns regarding treatment safety and efficacy. As guanfacine is a new medicine this will probably lead to parents being in more need of information and reassurance as there is less clinical experience which may lead to greater parental scepticism and greater fear with regard to new medicines.

5.6 Future clinical studies

Further research is required to understand the ‘pathophysiology’ of ADHD to understand whether a more thorough understanding of the different presentations of ADHD and also co-morbidity of other disorders may present more individualised ADHD treatment plans, whereby guanfacine treatment could be a first choice. Wider use of guanfacine treatment as a first line treatment could impact the decision-making of parents who may more readily choose to start their child with this guanfacine as opposed to stimulant medication or atomoxetine which all affect weight and growth development negatively.

The long-term effects of guanfacine on children’s development is unclear, with results of the phase IV study investigating the effect on cognitive development not due for completion until 2022 (3). New research in directly comparing the efficacy and safety of different ADHD medications is also required.

Further studies are required to investigate how ADHD treatment needs can differ over time, with the ADHD-symptoms varying over time and as seen in animal test subjects the response to guanfacine appeared to vary between adults and young rats and monkeys (3).

In general, it would be beneficial to have more research conducted about guanfacine that is independent of funding from Shire, including head-to-head comparison studies with other ADHD medications. The currently available studies about guanfacine that have been conducted were primarily funded by Shire and the motivation behind conducting these studies appeared to be in order to satisfy regulatory compliance required by the countries in which they were interested to achieve marketing authorisation for their product. The first studies were directed to achieve marketing authorisation in USA, the decision to apply for authorisation first in USA appears to have been due to the large market size in USA, although it can also seem that USA patients are a test centre for Europeans who have only recently authorised guanfacine.

6. Conclusion

6.1 Safety and efficacy of guanfacine

Guanfacine is authorised for monotherapy in Europe for ADHD child and adolescent patients, and was demonstrated as effective and safe for up to a 24-month treatment period (37, 38, 39). Guanfacine treatment is generally considered to be a safe and effective third choice treatment for children and adolescents with ADHD, after failed treatments with stimulants. A recent study has confirmed that guanfacine is effective in
prior-stimulant treated patients and ‘stimulant-naïve’ patients (31). Guanfacine demonstrated a significant improvement in ADHD symptoms; however, there appears to be a lack of clarity of the cognitive effect and also the effect on functioning which are important aspects of the ADHD disorder to address (3, 42).

6.1.1 Safety considerations

Guanfacine is considered safe providing risk prevention recommendations are taken, with common side effects including; somnolence, sedation, fatigue, headache and orthostatic hypotension. Cardiovascular adverse effects can occur including bradycardia and risk for pro-arrhythmic effect. Increased BMI can also occur as an adverse effect, requiring regular follow-up of growth and weight measurements of the patients. An important aspect to consider is that abrupt termination of treatment can cause a rebound effect, with risk for tachycardia and hypotension; careful adherence to medication is required.

6.2 Comparison of guanfacine with other ADHD medications

Due to lack of head-to-head comparative studies with guanfacine and other ADHD medications it was not possible to adequately fulfill the objective of comparing the efficacy and safety of guanfacine with other ADHD medications. However, the review articles which pooled in data from separate studies suggested that lisdexamfetamine was the most effective ADHD medication overall whilst guanfacine was the most effective non-stimulant. However, guanfacine had the highest reported dropouts due to adverse effects whereas methylphenidate had the lowest incidence of causing adverse effects which lead to drop-outs (46, 47).

6.3 Factors which influence parental decisions regarding ADHD medication

Fear of long-term ADHD medication, side-effects and risk for their child developing an addiction were found to worry parents. The parents also experienced negative stigma surrounding their child’s ADHD diagnosis and medication. The stress and exhaustion experienced by the parents coupled with their fears and experienced negative stigma contributed to problems with their child’s adherence to their ADHD pharmacotherapy.

The parents experience different stages of acceptance of their child’s ADHD medication, ranging from resisting starting ADHD medication to accepting the medication and managing adverse effects and issues surrounding treatment administration.

A collaborative approach to the treatment decision and adequate time taken to explain the diagnosis and treatment were positive factors.

6.3.1 Role of pharmacist

The difficulties facing parents who are deciding about ADHD medication for their child appear to be complex, with a great deal of support required. Pharmacists can offer support and guidance to ADHD patients and their parents, especially as they meet these patients before they start treatment and regularly during these long-term treatments. It is important for pharmacists to try to identify which stage of acceptance of their child’s ADHD medication the parents are in. It is important also to discuss adherence and to
give information with adequate complexity and detail. Hopefully pharmacists will help to increase parental understanding of their child’s ADHD medication by addressing worries regarding the medication and the associated side-effects which may in turn positively influence adherence to the treatment.

Acknowledgement

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## Appendix A

### Table 5. Literature search in PubMed.

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<td>(&quot;guanfacine&quot;[MeSH Terms] OR &quot;guanfacine&quot;[All Fields]) AND (efficacy[All Fields]) AND (&quot;2015/01/01&quot;[PDAT] : &quot;2017/04/03&quot;[PDAT])</td>
<td>33</td>
<td>2, 31, 46, 47</td>
<td></td>
</tr>
<tr>
<td>03/04/2017</td>
<td>(&quot;guanfacine&quot;[MeSH Terms] OR &quot;guanfacine&quot;[All Fields]) AND (&quot;methylphenidate&quot;[MeSH Terms] OR &quot;methylphenidate&quot;[All Fields]) AND comparison[All Fields]) AND (&quot;2015/01/01&quot;[PDAT] : &quot;2017/04/03&quot;[PDAT])</td>
<td>3</td>
<td>42, 46, 47</td>
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<tr>
<td>03/04/2017</td>
<td>(&quot;guanfacine&quot;[MeSH Terms] OR &quot;guanfacine&quot;[All Fields]) AND (&quot;atomoxetine hydrochloride&quot;[MeSH Terms] OR (&quot;atomoxetine&quot;[All Fields] AND &quot;hydrochloride&quot;[All Fields]) OR &quot;atomoxetine hydrochloride&quot;[All Fields] OR &quot;atomoxetine&quot;[All Fields]) AND comparison[All Fields]</td>
<td>9</td>
<td>46, 47</td>
<td></td>
</tr>
<tr>
<td>03/04/2017</td>
<td>(&quot;guanfacine&quot;[MeSH Terms] OR &quot;guanfacine&quot;[All Fields]) AND (&quot;safety&quot;[MeSH Terms] OR &quot;safety&quot;[All Fields]) AND (&quot;child&quot;[MeSH Terms] OR &quot;child&quot;[All Fields] AND &quot;child&quot;[MeSH Terms])</td>
<td>28</td>
<td>21, 43, 46, 47</td>
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</tr>
<tr>
<td>Date</td>
<td>Query Description</td>
<td>Results</td>
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<td>------------</td>
<td>-----------------------------------------------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>05/04/2017</td>
<td>Terms OR &quot;child&quot;[All Fields] OR &quot;children&quot;[All Fields]) AND (&quot;2012/04/05&quot;[PDat] : &quot;2017/04/05&quot;[PDat])</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10/04/2017</td>
<td>add[All Fields] AND (&quot;guanfacine&quot;[MeSH Terms] OR &quot;guanfacine&quot;[All Fields])</td>
<td>9, 42</td>
<td></td>
<td></td>
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<tr>
<td>10/04/2017</td>
<td>&quot;attention deficit disorder&quot;[All Fields] AND (&quot;guanfacine&quot;[MeSH Terms] OR &quot;guanfacine&quot;[All Fields])</td>
<td>170, 2, 9, 18, 21, 33, 36, 37, 38, 45</td>
<td></td>
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</tr>
<tr>
<td>11/04/2017</td>
<td>(&quot;methylphenidate&quot;[MeSH Terms] OR &quot;methylphenidate&quot;[All Fields] OR &quot;concerta&quot;[All Fields]) AND intuniv[All Fields]</td>
<td>4</td>
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<tr>
<td>11/04/2017</td>
<td>intuniv[All Fields]</td>
<td>16</td>
<td></td>
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<tr>
<td>19/04/2017</td>
<td>(&quot;parents&quot;[MeSH Terms] OR &quot;parents&quot;[All Fields] OR &quot;parent&quot;[All Fields]) AND decide[All Fields] AND (&quot;attention deficit disorder with hyperactivity&quot;[MeSH Terms] OR (&quot;attention&quot;[All Fields] AND &quot;deficit&quot;[All Fields] AND &quot;disorder&quot;[All Fields] AND &quot;hyperactivity&quot;[All Fields]) OR &quot;attention deficit disorder with hyperactivity&quot;[All Fields] OR &quot;adhd&quot;[All Fields])</td>
<td>7, 19</td>
<td></td>
<td></td>
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