Medication Adherence and Persistence in Children and Adolescents with Attention Deficit Hyperactivity Disorder (ADHD): A Systematic Review and Qualitative Update

Maite Ferrin (*) (**), Alexander Häge (**), James Swanson, Kirstie H. T. W. Wong, Ralf W. Dittmann, Tobias Banaschewski, David Coghill, Paramala J. Santosh, Marcel Romanos, Emily Simonoff, and Jan K. Buitelaar, on behalf the European ADHD Guidelines Group (EAGG).

(*) corresponding author; (**) joint co-first authors

MF: Child and Adolescent Mental Health Service, Barnet Enfield and Haringey NHS Trust, London, UK; ReCognition Health, London, UK.

AH: Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany

JS: Department of Pediatrics, University of California, Irvine, Irvine, California

KW: Department of Paediatrics and Adolescent Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong SAR, China and Research Department of Practice and Policy, UCL School of Pharmacy, Mezzanine Floor, BMA House, Tavistock Square, London WC1H 9JP

RWD: Paediatric Psychopharmacology, Dept of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany

TB: Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Germany

DC: Departments of Paediatrics and Psychiatry, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia; Murdoch Children's Research Institute, Melbourne, Australia

PS: Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK and South London and Maudsley NHS Foundation Trust, Maudsley Hospital, Denmark Hill, London, UK

MR: Department of Child and Adolescent Psychiatry, Center of Mental Health, University Hospital Wuerzburg, Wuerzburg, Germany

ES: King's College London, Institute of Psychiatry, Psychology and Neuroscience and Maudsley NIHR Biomedical Research Centre, London UK

JB: Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Centre, Nijmegen, The Netherlands; Karakter Child and Adolescent Psychiatry University Centre, Nijmegen, The Netherlands.

Members of the European ADHD Guidelines Group (EAGG) (in alphabetical order):

Baeyens, Dieter (Belgium)

Banaschewski, Tobias (Germany)

Bölte, Sven (Sweden)

Brandeis, Daniel (Germany and Switzerland)

Buitelaar, Jan K. (Netherlands)

Carucci, Sara (Italy)

Coghill, David (Australia)

Cortese, Samuele (United Kingdom) (EAGG chair)

Daley, David (United Kingdom)

Döpfner, Manfred (Germany)

Ferrin, Maite (United Kingdom)

Galera, Cedric (France)

Hollis, Chris (United Kingdom)

Holtmann, Martin (Germany)

Nagy, Peter (Hungary)

Purper-Ouakil, Diane (France)

Ramos-Quiroga, J. Antoni (Spain)

Romanos, Marcel (Germany)

Santosh, Paramala J. (United Kingdom)

Simonoff, Emily (United Kingdom)

Sonuga-Barke, Edmund (United Kingdom)

Soutullo, Cesar A. (United States)

Steinhausen, Hans-Christoph (Switzerland)

Thapar, Anita (United Kingdom)

Van den Hoofdakker, Barbara J. (The Netherlands)

Van der Oord, Saskia (Belgium)

Wong, Ian C. K. (Hong Kong)

Corresponding author:

Maite Ferrin

Email: maite.ferrin@nhs.net

Word count:

Abstract: 166 words

Manuscript: 10259 words

Tables:

- Table 1: ADHD medication adherence after 12 months across studies using the same definition of adherence (adherence = MPR≥80%)
- Table 2: ADHD medication persistence in days across studies that used the same definition of termination (=a gap of at least 30 days in prescription-filling activity)
    - 2a. Persistence (days): ADHD medication overall
    - 2b. Persistence (days): long-acting methylphenidate
    - 2c. Persistence (days): short-acting methylphenidate
    - 2d. Persistence (days) atomoxetine
- Table 3: Factors affecting treatment adherence

Figures:

- Figure 1: PRISMA chart
- Figure 2: ADHD medication adherence rates in percentage (adherence defined as MRP≥0.80) across studies at different time points
- Figure 3: ADHD medication persistence rates in percentage across studies at different time points

Abstract

Low medication-adherence and persistence may reduce the effectiveness of ADHD-medication. This preregistered systematic review (PROSPERO CRD42020218654) on medication-adherence and persistence in children and adolescents with ADHD focuses on clinically relevant questions and extends previous reviews by including additional studies. We included a total of n=66 studies. There was a lack of consistency in the measurement of adherence/persistence between studies. Pooling the medication possession ratios (MPR) and using the most common adherence definition (MPR≥80%) indicated that only 22.9% of participants had good adherence at 12-month follow-up. Treatment persistence on medication measured by treatment duration during a 12-month follow-up averaged 170 days (5.6 months). Our findings indicate that medication-adherence and persistence among youth with ADHD are generally poor and have not changed in recent years. Clinicians need to be aware that various factors may contribute to poor adherence/persistence and that long-acting stimulants and psychoeducational programs may help to improve adherence/persistence. However, the evidence to whether better adherence/persistence contributes to better long-term outcomes is limited and requires further research.

Keywords: adherence, persistence, ADHD medication, systematic literature review, children, adolescents

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental condition, with an estimated average prevalence rate of 5.2% among school-age children worldwide [1]. ADHD often persists into adulthood [2] and is associated with negative impacts on multiple domains, including peer interactions, academic performance, productivity at work, social and family adjustment [3], employment rate and income [4]. Furthermore, ADHD is associated with high rates of several somatic and psychiatric comorbidities [5, 6] and increased mortality [7]. Effective treatments can prevent or mitigate these adverse outcomes, with medication being a key intervention [8-10]. Meta-analyses of controlled studies of short-term treatment of children, adolescents, and adults with stimulant medication demonstrate large reduction of ADHD symptoms [11], less functional impairment, and better quality of life [12]. Longer-term benefits are less clear and the reasons for this remain a topic of debate [13, 14].

Medications should be used regularly and as prescribed since poor adherence to and low persistence of treatment can reduce the effectiveness of medication [15]. Medication-adherence describes the extent to which a patient follows the agreed-upon clinical recommendations about the timing, dosage, and frequency of medications [15]. Research into adherence to ADHD medication is complicated by different approaches to operationalize adherence (for details see table S1, supplementary material). Adherence is most often measured continuously reflecting the frequency of medication use defined as a percentage of days treated across an interval of time (i.e., from 0% to 100%) [16]. For observational follow-up studies, adherence may be specified as the percentage of days between assessments when medication was used. In prescription record studies, adherence is usually reported as the Medication Possession Ratio (MPR) or the Daily Possession Ratio (DPR) calculated as the total days' medication supply divided by the number of days between prescription refills [17]. Other authors have considered adherence as a category, and applied a cut-off as to whether an individual is "adherent or non-adherent" [18].

Persistence is usually described as a continuous variable reflecting a period of continued medication use from the point of initiation to the end of the observation period. This is based on a definition of "uninterrupted adequate medication use", with allowance for permissible gaps, which for prescriptions refills is typically set by the number of days beyond the date when the medication supplied would be consumed if taken as prescribed (e.g., 30 or 45 days) and represents an MPR < 1.0 (e.g., 0.8 or 0.7) [17, 19]. When the patient renews the prescription within the allowable gap, the patient is considered adherent (based on the assumed frequency of taking medication between prescriptions) and treatment as persistent (based on the number of refills of prescriptions without exceeding the permissible gap). Please note that the terms adherence and persistence are sometimes used interchangeably [16], however, they represent two different concepts, and persistent medication use does not necessarily mean adherent medication use. Therefore, patients who regularly skip doses may be considered non-adherent but persistent and continue treatment for the period indicated by their clinician [20].

Two systematic reviews on the topic of medication adherence and persistence in ADHD were published in 2013-2014 [17, 21]: The first review by Ahmed and Alsani [21] included nineteen studies; their inclusion criteria in relation to ADHD diagnosis and adherence/persistence definition were much stricter than the second review by Gajria et al. [17] that included a much larger set of 127 articles. Of the nineteen articles included in the review by Ahmed and Alsani fifteen were also included in Gajria et al. Both reviews concluded that adherence and persistence are poor in patients with ADHD and that several independent variables (most importantly tolerability, but also lack of symptom control, dosing inconvenience, social stigma, poor family support and patient´s attitudes) might influence adherence and persistence. Further, both reviews identified significant differences across studies in the definitions of adherence and persistence, the methods used to measure these complex concepts, and underlined that the long-term consequences of poor adherence and persistence required further research [17, 21-23]. These previous reviews, however, were limited by the fact that they included studies without a clear definition of adherence/persistence, included studies on patients without a clear diagnosis of ADHD, or did not consider data from randomized controlled trials with follow up periods (for details see table S2, supplementary material).

1.1 The current study

The current study presents an updated systematic review of ADHD medication adherence and persistence in children and adolescents. Our review considered all the studies identified by the two previous reviews mentioned above as well as randomized controlled trials with long follow up periods. Moreover, we extend previous reviews by including additional studies published over the period 2014-2022. We focus specifically on the age group of children and adolescents (<18 years), based on the assumption that clinically relevant aspects of adherence and persistence in this age group might differ significantly from those in adults. In contrast to previous reviews, we use a less restrictive search strategy in terms of study designs (e.g. also including data from RCTs). Based on the results of this review, we aim to address the following questions:

1) *What are the estimated rates of ADHD medication adherence and persistence in children and adolescents, and have these changed over the past 50 years?*
2) *Does adherence differ between different formulations (e.g., Immediate Release (IR) versus Extended Release (ER)) and class (e.g., methylphenidate, amphetamine, non-stimulants) of medication?*
3) *What factors predict ADHD medication adherence and persistence specifically in this age group and what needs to be considered by clinicians working with children and adolescents?*
4) *How many patients have brief/little or no medication use after it is prescribed? And how many patients have repeated episodes of sporadic medication use?*

5) *What interventions might enhance treatment adherence in this specific group of patients?*
6) *Is medication adherence and persistence in children and adolescents with ADHD related to better long-term outcomes?*

Finally, this review aims to make recommendations as to how adherence and persistence should be operationalized and measured in future studies and what should be next steps to take in this field of research.

The study was registered to the PROSPERO register on 9th December 2020 (CRD42020218654).

2. Methods

2.1 Search

A systematic literature review was initially performed on 28th January 2020, by searching six main electronic databases using Healthcare Databases Advanced Search (HDAS); MedLine including In-Process and Other Non-Indexed Citations, (January 1946–January 2020); EMBASE (January 1974–January 2020); PsycINFO (January 1806– January 2020); PubMed, CINAHL, AMED (January 1985–January 2020); and Cochrane Database of Systematic Reviews (January 2005– January 2020). As the review process was temporarily interrupted because of the COVID-19 pandemic, the search was updated on 31st December 2021 (first update) and on 23rd May 2023 (second update). The search terms used are shown in table S3, supplementary material.

2.2 Screening

Publications were screened at two levels. First, inclusion/exclusion criteria were applied at the title and abstract level. Second, the full text of those passing through the initial screen were retrieved and reviewed against the selection criteria. If excluded at this stage the reason for their exclusion was recorded for each article failing the second level of screening. Two authors from the writing group conducted the screenings independently, and a third researcher was consulted to arbitrate disagreements over study inclusions when needed. To ensure all relevant studies were included, original studies identified by prior reviews were retrieved and examined to identify any additional original studies previously not included. Similarly, multiple publications and kin studies were identified to avoid duplication.

2.3 Inclusion/exclusion criteria

Original publications retrieved from the search were screened, and studies were included if they met the following criteria:

1) Participants under the age of 18 years.
2) A diagnosis of ADHD of any subtype (DSM-defined ADHD or ICD-defined hyperkinetic disorder, as well as historic alternative diagnostic labels; we excluded minimal brain dysfunction). There was no restriction on ADHD subtype/presentation, gender, IQ or socioeconomic status of participants. As for comorbidities, we also included studies in which some, or all, participants had psychiatric or neurological comorbidities (except genetic syndromes). Pharmacological treatments for these comorbidities were allowed.

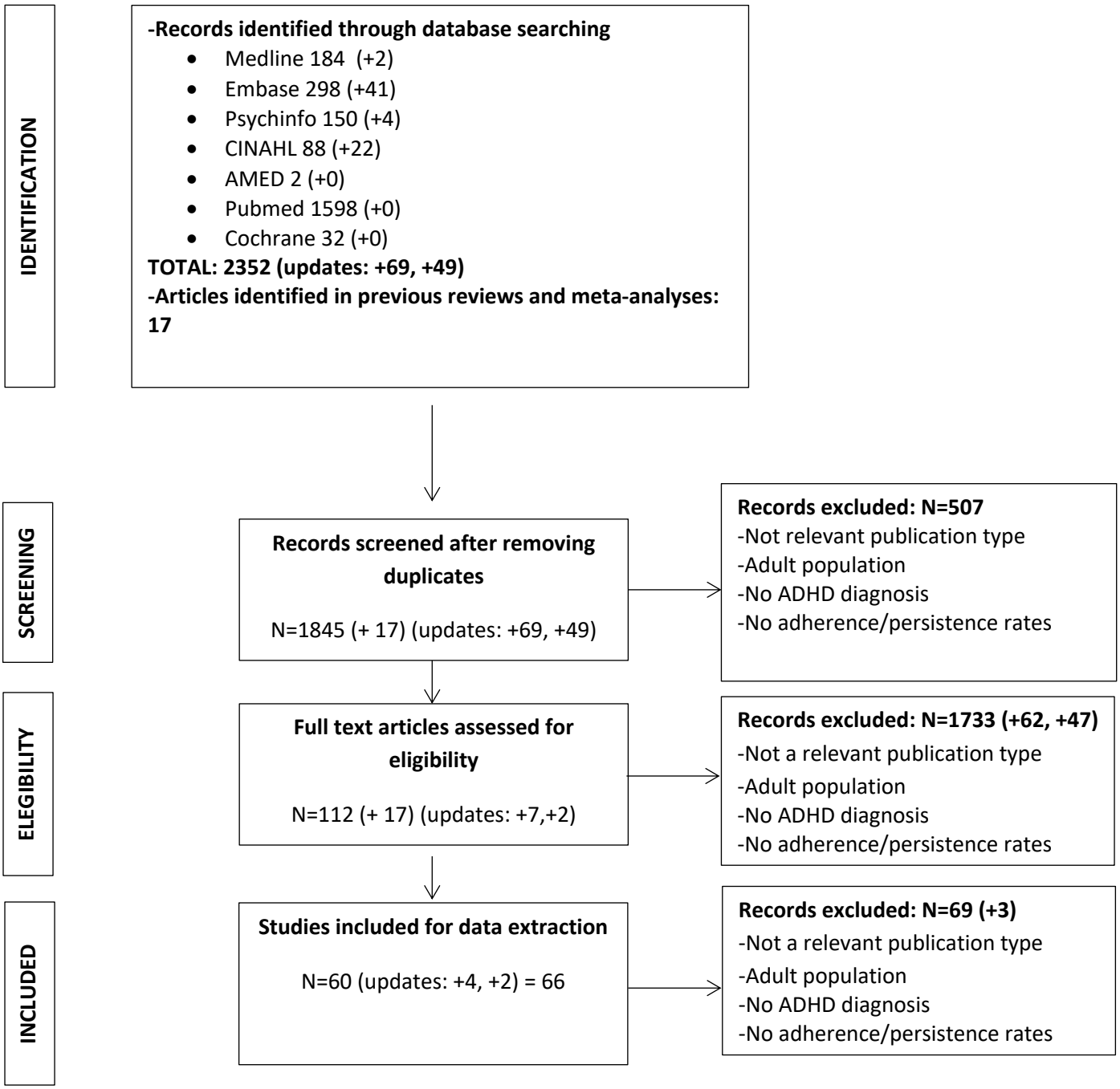
3) Prescription of stimulants (methylphenidate, amphetamines, dexamphetamine, lisdexamphetamine, pemoline) or non-stimulants (atomoxetine, guanfacine, clonidine) or any medication for ADHD (regardless of the treatment duration).
4) At least one outcome reporting treatment adherence, treatment compliance or treatment persistence. A definition of treatment adherence, treatment compliance or treatment persistence was provided, or in those studies where the definition was not clear the authors clearly stated how adherence/compliance/persistence was assessed.
5) Given the lack of randomized controlled trials (RCTs) with adequate systematic data on treatment adherence/compliance/persistence, open-label and double-blinded study designs without a control group were also included.

The following studies were excluded:

1) Studies not written in English.
2) Studies that included children/adolescents and adults, without a clear description of data/results in the first group.
3) Previous reviews and meta-analyses, conference abstracts, study protocols, dissertation abstracts.
4) Studies reporting only on discontinuation rates.

Our review followed the reporting guidelines recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (http://www.prisma-statement.org/) (see figure 1).

FIGURE 1: PRISMA chart



2.4 Data extraction

Data was extracted from original research articles meeting the selection criteria, which included publication details, adherence/persistence definition, method/s used, and adherence/persistence rates (see table S4, supplementary material).

2.5 Data synthesis

Data were synthesized to explore the consistency of adherence and persistence definitions and the methods used to measure these concepts. A qualitative summary was constructed for estimates of adherence/persistence from the studies included. Data were synthesized for the following outcomes: 1) country; 2) sample size; 3) participants age; 4) study type; 5) type of ADHD medication; 6) adherence/persistence measures; 7) adherence/persistence definitions; 8) results. Following previous literature, adherence was expressed using the MPR/DPR, and it was calculated as the ratio of time (number of days) covered when medication was taken as recommended by the prescriber, divided by the time between subsequent prescriptions. The percentage was given as a continuous variable (%), and/or as a dichotomous variable (e.g., "good" or "poor" adherence), depending on what was stated in each study [16]. Persistence was defined as the time from initiation until discontinuation [16], or the time taking the medication without exceeding permissible gaps. Prescription gap represented gaps in medication supplies during a defined period following a prescription. The study length was specified as the time between the earliest and the latest dates of prescriptions in the databases. Within a study period, a patient can have one single treatment episode, or multiple episodes. For each episode, a delay before treatment initiation can be observed. Persistence represents the time between the first initiation and the last cessation (when all the episodes are considered), or the duration of the first episode (when only the first episode duration is considered).

A quantitative analysis was performed using data from subsets of studies that had common definitions for adherence and persistence and that implemented comparable measure methods (i.e., had common frequency cut-offs and follow-up periods). For various patient subgroups, pooled estimates of treatment duration were calculated as the weighted average across studies by sample size. These pooled estimates were then compared by medication class (stimulants versus nonstimulants) and formulation (long-acting versus short-acting).

3. Results

The initial search identified a total of 2,352 citations. The first full-text extraction identified 60 publications meeting all selection criteria. The updated search identified an additional 69 articles, with four additional articles meeting inclusion criteria. The second updated search identified further 49 articles, with two additional articles meeting inclusion criteria (see figure 1).

The final list of the 66 original studies included in this review and the outcomes for each study are shown in the supplementary material (table S4). Of these 66 studies, 31 were published 2014 and later, and therefore after the systematic reviews by Gajria et al. [17] and Ahmed and Aslani [21].

3.1 Description of the included studies

Thirty-four papers described retrospective studies of databases from health insurance registries, drug registries or medical records. The other 32 were prospective studies. Most of these used data from direct questioning of patients/parents or clinicians, four used pills counting [24-27] and two used a medication event monitoring system (MEMS) [26, 28].

Thirty-eight studies focused on medication adherence, 18 studies measured persistence, and ten studies reported data on both, adherence, and persistence. Study duration, definitions of adherence and persistence, and measurement methods varied considerably across studies. The study length for prospective studies measuring medication adherence varied from 1 week [28] to 50 months [29]; the most common follow-up period across 12 studies was of 12 months. Adherence was reported as a continuous measure of adherence on a scale from 0 to 1 by some authors [30-35]. However, other studies used a categorical definition of treatment adherence using a threshold of ≥0.80 [24, 26, 30, 36-44] or ≥0.70 [32, 42, 45-48].

Most studies on medication persistence reported "persistence" as treatment duration or the time during which patients remained on the initial ADHD therapy from the date they initially started it until discontinuation. There were, however, significant differences in the permissible gap length, which varied from 14 days [49] to 180 days [50-52]. Studies in which adherence was measured used different methods for this purpose. Sometimes different measurement methods were used within one study. For instance, Charach et al. [28] found similar adherence rates from semi-structured phone interviews and MEMS. Yang et al. [26] who compared three different methods to measure adherence found that estimates of adherence rates were higher for pill counts than for MEMS or patient's or clinician's report. In the Multimodal Treatment for ADHD (MTA) study, adherence was assessed using saliva tests and parent reports. The comparison showed higher adherence rates in parent report compared to adherence

based on saliva test [39, 53, 54]. Fried et al. [55] compared data from electronic medical records (EMR) and an innovative SMS text messaging system individualized for patients initiating stimulant medication [56] and reported higher adherence estimated by SMS than EMR.

Overall, this review found considerable heterogeneity across different studies, which used different methods to measure adherence and persistence and to report outcomes. Similarly, substantial differences in medication classes across the studies were observed. Some studies examined adherence and persistence rates among stimulant and non-stimulant users, whereas 20 studies reported adherence and persistence rates for stimulants only [25-28, 32, 33, 36, 39, 40, 57-68]. One study reported results for non-stimulants only [69].

3.2 Quantitative and qualitative review and key questions:

A summary of the current evidence found for the questions mentioned above is presented here. More detailed responses are found in the supplementary material.

3.2.1 What are the estimated rates of ADHD medication adherence and persistence in children and adolescents, and have these changed over the past 50 years?

3.2.1.1 Adherence

Considering all available studies on ADHD-medication adherence in children and adolescents we found adherence rates between 15% and 100% (with very high rates of adherence in small sample trials and mostly very short observation periods; for details see table S4). As mentioned above, study length for prospective studies varied significantly, with the most common follow up period of twelve months. For patients who remained in study, reported adherence rates at twelve months ranged between 21.8% [70] to 93.9% [71] for stimulants, and from 54.9% [69] to 88.0% [71] for atomoxetine. However, these results were based on different assessment-methods and on different definitions of adherence. The most used definition of adherence was categorical, with adherence defined as medication possession ratios (MPR) of ≥80%. Figure 2 summarizes the rates of 'good' adherence (=MPR ≥0.80) according to the time at which it was measured in different studies.

FIGURE 2: ADHD medication adherence rates in percentage (adherence defined as MRP≥0.80) across studies at different time points. (MRP=Medication Possession Ratio).

Pooling the medication possession ratio (MPR) findings from the three studies (one included MPH only and two combined stimulant and non-stimulant medications) that measured adherence over a 12-month period [30, 40, 42] and used the most common adherence definition (MPR≥80%) indicated that 22.9% of participants were adherent at 1 year follow up (see table 1).

TABLE 1: ADHD medication adherence after 12 months across studies using the same definition of adherence (adherence = MPR≥80%)

Study	Hodgkins 2011	Hong 2014	Hong 2016
Sample size	3 614	300	15 133
Adherence rate after 12 months	39.5 %	47.3%	18.48 %
Pooled adherence rate	22.92%		

MPR: Medication Possession Ratio

3.2.1.2 Persistence

Definitions of persistence also varied within the different studies. Most studies reported persistence as treatment duration or the time during which patients remained on the initial ADHD therapy from the moment they initially started it until they discontinued. However, there were significant differences in the permissible gap length, which varied from 14 to 180 days [50-52]. Several studies reported persistence rates at different time points summarized in Figure 3.

FIGURE 3: ADHD medication persistence rates in percentage across studies at different time points.

Eight studies in total employed the same definition of termination (a gap of at least 30 days in prescription-filling activity) [20, 31, 44, 58, 59, 72-74]. Pooling of persistence estimates was feasible for five of these studies that combined all types of medications [20, 44, 58, 72, 74], for four studies using long-acting methylphenidate [31, 58, 59, 73], for two studies using short-acting methylphenidate [58, 59] and for two studies that used atomoxetine [31, 58]. Persistence ranged from 91.5 days (for short-acting methylphenidate) to 170.6 days (when all the medications were combined); persistence was 154.1 days for long-acting MPH and 155.2 days for atomoxetine (for details see table 2).

TABLE 2: ADHD medication persistence in days across studies that used the same definition of termination (=a gap of at least 30 days in prescription-filling activity)

2a. Persistence (days): ADHD medication overall

Study	Raman 2015	Perwien 2004	Palli 2012	Bhang 2017	Brinkman 2017
Sample size	1,314	715	4,6135	69,631	1,352
Mean days of persistence	321	200.9	97.83	216.9	110
Pooled persistence	170.63 days				

2b. Persistence (days): long-acting methylphenidate

Study	Christensen 2010	Marcus 2005	Palli 2012	Greven 2017
Sample size	21,386	3,444	3,3561	488
Mean days of persistence	232.39	140.30	104.96	203.2
Pooled persistence	154.12 days			

2c. Persistence (days): short-acting methylphenidate

Study	Palli 2012	Marcus 2005
Sample size	8,260	8,093
Mean days of persistence	79.97	103.4
Pooled persistence	91.56 days	

2d. Persistence (days) atomoxetine

Study	Christensen 2010	Greven 2017
Sample size	35123	486
Mean days of persistence	154.3	222
Pooled persistence	155.22 days	

Considering all available data, it remains difficult to determine whether adherent behaviour and/or persistence of ADHD medication use had changed over the years. This literature search revealed only two studies published before 2000 [25, 75], both of which reported relatively high adherence rates of ≥67%. However, given the study designs and definitions of adherence in these studies, it becomes obvious that these results cannot be compared with results from later studies (for details see table S4). Although studies over the past two decades have consistently emphasized that lack of adherence was and is a highly relevant clinical problem and frequently occurs, adherence and persistence rates are mostly difficult to compare. When focusing on studies that took comparable approaches and used the same definitions for adherence or persistence no clear trend indicating an increase or decrease of adherence or persistence could be found. Furthermore, we found only two studies with a longitudinal design trying to examine trends in adherence/persistence, reporting results trending in opposite directions: Lambert et al. [64] reported a small decrease in persistence of medication use, defined as duration of the first episode of use, in Australia from an average of 2.01 years during 1990 to 1999 to 1.79 years from 2000 to 2010. In contrast, in the UK Wong et al. [50] reported a 40% decrease in the medication discontinuation rate comparing results from 1999 to 2003 to those from 2004 to 2006.

3.2.2 Does adherence and persistence differ between different formulations (e.g., Immediate Release (IR) versus Extended Release (ER)) and class (e.g., methylphenidate, amphetamine, non-stimulants) of medication?

Due to substantial differences in the definition of adherence or persistence and the methods used to measure adherence, it is difficult to compare adherence and persistence across studies with respect to different ADHD medications and formulations in an objective way. We found four studies [31, 37, 59, 76] comparing adherence and/or persistence of short acting (e.g. immediate release methylphenidate) vs. long acting ADHD medication (e.g. extended release methylphenidate), and six studies comparing different types of ADHD medication (four studies [20, 31, 36, 62] comparing different types of psychostimulants including methylphenidate and dex-amphetamine, and three studies [30, 31, 77] comparing stimulants vs. non-stimulants). As result of these comparisons, long-acting formulations were found to be associated with better treatment adherence and persistence compared with short-acting or immediate release agents. Furthermore, immediate-release methylphenidate and dex-amphetamine seem to have similar rates of adherence and persistence. Regarding the comparison of adherence and persistence between stimulants and non-stimulants, there was one study suggesting that persistence with non-stimulants is lower than with stimulant and two studies comparing stimulants and atomoxetine with divergent results not allowing clear conclusions. In addition, several studies showed that multiple administrations per day of ADHD medication is associated with lower adherence and persistence [57, 60, 61]. More details about the different findings and studies can be found in table S6.

iii) What factors predict ADHD medication-adherence and persistence specifically in this age group and what needs to be considered by clinicians working with these patients?

We found a range of studies that identified factors associated with improved or poorer medication-adherence or persistence in ADHD. In addition to single findings, there were multiple replicated findings, but also studies with contradictory results. Table 3 gives an overview of factors affecting treatment adherence, more detailed information on the different studies and findings is given in Table S11. Several studies [24, 30, 36, 37, 52, 57-59, 68, 72, 77, 78] showed that adherence and persistence are reduced in adolescents compared with children, supporting the hypothesis that clinicians should pay particular attention to adolescent patient groups in this respect. In addition, some studies found that patients' subjective attitudes and health beliefs are relevant, and, experience of stigma, a less trustful doctor-patient relationship and low family support are associated with lower adherence [29, 50, 79-81]. Oppositional defiant disorder (ODD) as a common comorbidity of ADHD was associated with lower adherence in some studies [46, 57, 82], whereas some other comorbidities, such as learning disabilities, anxiety and pervasive developmental disorders were associated with better adherence possibly due to a closer monitoring [24, 28, 38, 46, 58, 82]. Single studies showed associations between barriers to access treatment services and less specific care with lower adherence [62, 83-86], and between lower socioeconomic status and lower adherence and persistence [34, 87]. For instance treatment provided by ADHD specialists (e.g. child psychiatrists) rather than by community primary care providers seemed to have a positive effect on treatment adherence, possibly because specialists were more able to provide a close titration and careful monitoring of ADHD medications. As stated earlier, complex treatment regimens (especially taking multiple tablets per day) were also associated with lower adherence, as was low treatment response [24, 50, 57]. Some studies suggest female gender to be a factor associated with better treatment adherence, but the data so far is inconsistent with some other studies suggesting male gender to be associated to better rates [24, 50, 64]. Furthermore, surveys among treatment providers in different countries suggest that differences in country comparisons must also be assumed and regional differences considered (see table S11).

TABLE 3: Factors affecting treatment adherence

Patient-related factors	Younger age at treatment onset
	Comorbid ODD
	Lower IQ
Family-related factors	Poor family support, impaired family dynamic
	Family history of ADHD
	Lower socioeconomic status
Medication-related factors	Long acting formulations
	Multiple dosing
	Ineffectiveness and side effects
Other factors	Negative opinion about medication
	Perceived stigma
	Less trustful physician-patient relationship
	Treatment provided by (ADHD) specialists

ODD = Oppositional Defiant Disorder; IQ = Intelligence Quotient; ADHD= Attention Deficit Hyperactivity Disorder

_____ Factor related to increased medication adherence

_____ Factor related to reduced medication adherence

More detailed information including references of all studies providing supporting evidence, can be found in the supplementary material (Table S11)

iv) How many patients have brief/little or no medication use after it is prescribed? And how many patients have repeated episodes of sporadic medication use?

We found a number of studies [72, 88-91] from different countries reporting on rates of little or brief medication use in ADHD patients (table S7). The proportion of patients with brief medication use in these studies varied between 20.9% and 78%, with most studies showing that about 50% used ADHD medication for a short period only. However, definitions of “short” or "brief” medication use differed considerably across studies. Most commonly, medication use of less than one year was defined as "brief use". However, studies were also found that defined “brief use” as the use of less than 6 months or even less than 90 days. Detailed information on the studies and their outcomes can be found in table S7.

When considering studies that examined medication adherence and/or persistence over the long-term, it is particularly important to consider whether patients with short/brief medication use were included and considered for the analysis of the data. Since the proportion of patients with brief medication use seems high, long-term observational studies including these patients result in much higher rates of non-adherence. A comparison of long-term observations in which patients with brief medication use were included and those in which they were excluded can be found in table S8.

Repeated episodes of starting and stopping medication use can also distort overall estimates of adherence and persistence in follow-up studies that assess use over time in different individuals, since the percentage of cases being treated at each assessment point mixes cases with different patterns of starting and stopping medication.

Studies of prescription records for children in different countries [78, 92], observational follow-up studies [46, 82], and the multi-site MTA study [87, 93], suggest that up to 40-50% of all cases have sporadic use only. Further studies showed that a relevant proportion of patients (up to 30%) had multiple treatment courses with typically significant gaps of three months or more in between [50, 72].

v) What interventions might enhance treatment adherence in this specific group of patients?

Although the search of this review was not primarily designed to seek studies that examined the effectiveness of interventions to improve medication adherence in children and adolescents, we did find many studies that described and/or examined such interventions/approaches. Table S12 gives an overview of our findings. An important approach to improve medication adherence is psychoeducational programs designed to provide patients and families with a comprehensive understanding of both ADHD and ADHD medication. In this regard, several randomized controlled trials and one systematic review were found, suggesting that such psychoeducational programs result in significant improvement in

medication adherence compared with control groups (for details/references, see Table S12). Furthermore, we found two randomized controlled trials investigating the effect of interventions with a digital reminder function (via SMS and mobile phone application, respectively) showing that these interventions were also helpful in improving medication adherence [27, 55]. Other approaches are less well studied and are based more on clinical experience and the knowledge of factors that contribute to poor adherence. In this context we found recommendations to improve adherent behavior in ADHD patients by including youths as active participants in their own treatment decision and by following a personalized treatment with regular contacts and a careful titration and monitoring of side effects.

vi) Is medication adherence and persistence in children and adolescents with ADHD related to better long-term outcomes?

The question of whether improved adherence contributes to improved long-term outcomes is clinically highly relevant, however, time data on this are extremely limited. A national survey involving children with poor adherence who were switched to prolonged release methylphenidate showed that worse adherence was associated with more severe ADHD symptoms [57]. Interestingly a systematic review also found an association between suboptimal adherence and worse clinical outcomes [94]. However, results from the MTA follow-up study do not support the hypothesis that better medication adherence and/or persistence contribute to better long-term outcomes in ADHD. Although previous analyses of the MTA showed that long-term persistent (defined as > 1 year) stimulant treatment was associated with better outcomes compared to less persistent treatment, the positive effect of stimulant treatment dissipated in the MTA follow-up phase, as patients moved from one initial group to the other, but adjustment for current and history use of medication did not have a significant effect on extended long-term outcome.

Discussion

Our review of medication adherence and persistence in children and adolescents with ADHD found adherence rates ranging from 100% to 15% (with the former based on a small sample and very short observation period) and average persistence of 91.5 days for short-acting stimulants and 154.1 and 155.2 days for long-acting stimulants and atomoxetine, respectively. However, there was enormous variability in definitions of adherence and persistence, methods of measuring adherence, and study designs. Our quantitative analysis of medication adherence from studies with the most used definition of adherence (MPR of ≥80%) and observation period (12 months), found that after one year, less than 23% of patients showed good adherence. Overall, data show that medication adherence in children and adolescents with ADHD must be considered very poor and persistence on average short.

Moreover, although comparability of data is very limited, results on ADHD medication adherence over the last decades do not suggest that adherence has changed (improved or worsened) in any relevant way, which underlines that adequate solutions for the issue of non-adherence in ADHD still have not been found. Especially when interpreting data from prospective studies, the substantial number of patients with brief or with sporadic medication use must be considered.

We found a variety of factors associated with better adherence and persistence including younger age, using long-acting formulations and the presence of various comorbidities [21, 24, 57, 82]. Furthermore, factors such as patients' personal attitudes toward treatment, beliefs about ADHD and ADHD medications, the prescriber-patient relationship, and the amount of support from the patient's environment also seem to be relevant and therefore need to be considered. The impact of gender differences and the presence of comorbidities on adherence is still not sufficiently understood.

Since various factors may contribute to poor treatment adherence, different approaches/interventions might help to improve it. In our review, we found the best evidence in this respect for psychoeducational programs. In addition, a simple medication regimen (preferably a single dose per day) seems to contribute to better overall adherence. Moreover, technology-based and digital interventions may be helful. Overall, the current data suggest that clinicians should focus particularly on thorough psychoeducation, regularly review adherence of all patients especially during the first months, consider making use of reminder features for patients and individually examine reasons for poor adherence if any evidence of lack of adherence should emerge during treatment. Psychoeducation has a special role in this context, as it is an obligatory component of any ADHD therapy [8]. Overall psychoeducation programs were found to be associated with several positive outcomes, including improvements in medication-adherence, but also improvements in ADHD symptoms, patient´s behavior and parent and child satisfaction [48, 95-98]. However, as van Langen et al. pointed out, psychoeducational programs can use biomedical as well as psychosocial perspectives that sometimes result in internal conflicts causing confusion, misrepresentation and decontextualization of ADHD [99].

Overall, there are several elements of psychoeducation that can be considered important in terms of treatment adherence and persistence. First, with regard to medication adherence, it seems helpful if psychoeducation is based on a biopsychosocial and medical model of understanding mental disorders and emphasizes the need for medication treatment in moderate to severe cases [96, 97]. Second, psychoeducation programs should be conducted on the basis of mutual participation and understanding between clinicians and participants, and not just as one-way instruction [100]. Finally, it may be helpful to design psychoeducation as a structured multi-session intervention with a particular focus on treatment options, adherence and compliance. It is helpful if both a practical and theoretical approach is offered to help participants understand and empower them to deal with the symptoms and consequences of their disorder [96, 97, 100].

In many ways, our results are consistent with those of former reviews [17, 21] on adherence and persistence in ADHD, although these did not include recent studies, did not focus specifically on children and adolescents, and differed from our review in terms of inclusion and exclusion criteria. However, past reviews also showed medication adherence in children and adolescents with ADHD to be low and persistence to be relatively short [17, 21]. In accordance with our findings previous reviews also found that various factors may contribute to poor adherence and that in particular, long-acting stimulants and psychoeducational programs can improve adherence and persistence to medication overall. In general, it is recommended that clinicians should examine reasons for non-adherence individually, especially considering that not only the efficacy and tolerability of medication can be important for adherence, but also subjective attitudes, beliefs, health beliefs, and the influence of family and peers. For this reason, it seems essential that clinicians invest enough time to establish a positive physician-patient relationship and to sufficiently understand their patients' (and parents') attitudes and views. Patients should be asked about any side effects, about their knowledge and opinions on medication and whether they are happy to take them, as these questions can predispose to poor adherence and/or persistence. Clinicians should also consider that indicators of poor adherence/persistence to ADHD medications can be a resourceful tool to identify the group of young people who need specific support and additional interventions.

In contrast to previous work, we also questioned whether lower adherence has relevant effects on long-term outcomes and found that the evidence in this regard is inconsistent and very limited. Therefore, future research on adherence in ADHD should further investigate this aspect by conducting long-term observation studies.

Low adherence and persistence to medication are common not only in ADHD but also in many other chronic disorders. Most extensively this issue has been studied in patients suffering from asthma, with

studies suggesting that only about 50% of patients with asthma properly adhere to treatment [101]. Other studies highlight that medication adherence for further serious medical conditions seems equally poor; using a urinary assay to measure adherence, a study of children with leukemia found an average adherence of 58% [102]. A systematic review of pediatric transplantation found that medication adherence varied from 22 to 97% depending on the assessment methods between studies, with two thirds of the studies that found adherence to be lower than 80% [103]. Another review demonstrated that the prevalence of non-adherence measured by MEMS was 44% among children with acute lymphoblastic leukemia, and that 47% of the relapses observed among children entering remission were attributable to non-adherence [104]. Such findings illustrate that medication non-adherence in children and adolescents is widespread in a wide variety of medical conditions. However, when comparing findings from somatic disorders to the results of our review it is important to note that the consequences of suboptimal adherence in many somatic disorders may be different, possibly in part more serious than in ADHD, with sometimes life-threatening complications. Studies and reviews on medication adherence in patients with diabetes for example have shown that non-adherence to diabetes-medication is not only associated with poor glycemic control, but also clearly linked with increased emergency room visits, hospitalization and mortality [105-110]. Medication non-adherence in patients suffering from epilepsy or asthma – which was found to be especially poor in adolescents - was also found to be associated with mortality and an increased risk of sudden death [111-115]. One may argue that untreated ADHD is also associated with long-term negative consequences, a higher risk for accidents and premature death [7, 116], however, it remains unclear whether suboptimal medication-adherence significantly increases these risks compared to completely adherent behavior in the long-term.

Since the long-term consequences of suboptimal adherence in ADHD patients have not been well enough studied, the question arises whether clinicians should not tolerate a certain degree of (partial) non-adherence in patients with ADHD. Moreover, as the needs for ADHD medications may vary considerably in each individual over time and depend on day-to-day requirements, it may be acceptable for some patients to interrupt or reduce medication on certain occasions (e.g., weekends, school breaks or when taking the medication could be problematic such as when visiting a party, or at certain sporting events). In line with this, although some data suggest that long-term treatment with ADHD medications is associated with positive outcomes [117], and medication adherence may contribute to this, future studies should also examine whether some tolerance on the prescriber's side for suboptimal adherence may not be preferable and whether pragmatic, individualized solutions may not be better than striving for complete adherence.

The present findings need to be interpreted in the context of some limitations. First, we showed that the definitions of adherence and persistence as well as the methods to measure adherence varied significantly which limits the comparability of study results and the possibility for meta-analytic approaches. Second, the very common phenomenon of short-term or sporadic use of ADHD medications

is considered and evaluated differently across studies, which in turn limits the comparability of these study findings. Finally, even if our review intended to respond to several relevant questions that can be paramount for the everyday practice, scientific evidence was limited in some of these questions and therefore conclusions had to be extrapolated.

With regard to future research on medication adherence in children and adolescents with ADHD, further prospective, observational studies are needed for which the following should be considered. Since adherence and persistence are different concepts, both of which are highly relevant, studies should ideally examine both. In addition, as an important number of cases have brief medication use and discontinue medication during the first months or have bouts of medication use, it is important to ensure a sufficient observation period of at least one year. Since there is no gold standard for the assessment of adherence and different studies have shown that different methods can lead to different results, we recommend a multi-measure approach, ideally including at least one so-called objective measurement (for an overview of medication adherence measures and the different advantages and disadvantages, see table S1, for more details also see Lam and Fresco[118]). Furthermore, the group of patients who discontinue an effective medication after a very brief period of use should be further investigated to better understand common reasons for early discontinuation and predictors for brief use. In addition, it seems crucial to thoroughly investigate the impact of cultural and social factors (such as prevalent health beliefs and stigmatization tendencies) and the healthcare landscape across different countries (including medication availability, access to specialists, the frequency of outpatient visits) on adherence of patients with ADHD. Finally, to evaluate the effects of interventions to improve medication adherence (see also Parkin et al. [119]) further randomized controlled trials are needed. Considering that reasons for non-adherence may significantly differ on an individual level most likely multiple different approaches that are aiming to improve adherence and persistence may be needed.

Conclusion

The present systematic review shows that poor adherence and persistence to ADHD medication is common in children and adolescents and has been maintained in the last 30 years. Clinicians should be aware of that and monitor adherence and persistence carefully, especially during the first month of treatment. We found various factors that may contribute to poor adherence or short persistence and different approaches that may help to improve adherence and persistence overall. However, given the complexity of the phenomenon, an individualized approach seems most promising. Moreover, further research is required to investigate whether better adherence and longer persistence contribute to better long-term outcomes.

Acknowledgements:

We would like to express our appreciation to Dr. Magdalini Vasileiou, Librarian Team Leader at Barnet, Enfield and Haringey Mental Health NHS Trust, for her assistance in conducting the literature search. We would also like to thanks Medice for supporting Dr Ferrin during the 2021 ISBEA meeting, where she presented the preliminary results of this review.

Author Contributions:

MF, AH, JS, KW, RWD, TB, DC, PS, MR, ES, and JB contributed to the study conception, literature search, quality assessment, and data extractions. Data analysis and interpretation were performed by MF, AH and JB, with input from all authors. The first draft of the manuscript was written by MF, and subsequent revisions were made by all authors. All authors read and approved the final version of this manuscript.

Declarations:

Conflicts of interest:

Maite Ferrin has been attending ISBEA meetings in 2021, 2022 and 2023; she has been a member of the advisory board for Novartis in 2021 and Neuraxpharm International in 2023.

Alexander Häge has been in the past 3 years a member of advisory board of / and/or speaker for Takeda and Medice. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

James Swanson reported honoraria, consulting fees, and support for travel to and presentations at professional meetings by Medice, NLS, and Takeda; a patent for Pixel Averages for Auxological Assessment (PIXA); a patent pending for Prevention of Accumulated Tolerance for Stimulant Medication for Treatment of ADHD (PATSMTA); and previous but not current or recent support from grants and contracts for studies of treatment of attention-deficit/hyperactivity disorder.

Kirstie H. T. W. Wong: None

Ralf W. Dittmann has received compensation for serving as consultant or speaker, or he or the institution he works for have received research support or royalties from the organizations or companies indicated: EU (FP7 Programme), US National Institute of Mental Health (NIMH), German Federal Ministry of Health/Regulatory Agency (BMG/BfArM), German Federal Ministry of Education and Research (BMBF), German Research Foundation (DFG), Volkswagen Foundation; Boehringer Ingelheim, Ferring, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Servier, Shire, Sunovion/Takeda and Theravance. He was a former employee in clinical CNS research of Eli Lilly until Aug 2008, and owns Eli Lilly stock

(small part of the respective annual salary). Since then, he has fully been affiliated with the Department of CAP, CIMH, Med Faculty Mannheim, University of Heidelberg, Germany.

Tobias Banaschewski served in an advisory or consultancy role for eye level, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche and Takeda. He received conference support or speaker's fee by Janssen, Medice and Takeda. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press; the present work is unrelated to these relationships.

David Coghill has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Medice, Novartis, and Servier. He has received royalties from Oxford University press and Cambridge University press. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has received research support during this period from the Australian National Health and Medical Research Council and the Royal Children's Hospital Foundation and funding for the current study from the European Commission

Paramala J. Santosh is the CEO and shareholder of HealthTracker Ltd and has received research funds from Newron Pharmaceuticals SpA, GWPharma, and Anavex Life Sciences Corp.

Marcel Romanos: none

Emily Simonoff: none

Jan K Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda, Roche, Medice, Angelini, Boehringer-Ingelheim, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

Ethics approval: no ethics approval was required

Informed consent: not applicipal

Consent for publication: not applicipal

References

1. Polanczyk, G.V., et al., *ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis.* Int J Epidemiol, 2014. **43**(2): p. 434-42.
2. Biederman, J., E. Mick, and S.V. Faraone, *Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type.* Am J Psychiatry, 2000. **157**(5): p. 816-8.
3. Barkley, R.A. and M. Fischer, *Hyperactive Child Syndrome and Estimated Life Expectancy at Young Adult Follow-Up: The Role of ADHD Persistence and Other Potential Predictors.* J Atten Disord, 2019. **23**(9): p. 907-923.
4. Pelham, W.E., et al., *The long-term financial outcome of children diagnosed with ADHD.* J Consult Clin Psychol, 2020. **88**(2): p. 160-171.
5. Faraone, S.V., et al., *The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder.* Neurosci Biobehav Rev, 2021. **128**: p. 789-818.
6. Kittel-Schneider, S., et al., *Non-mental diseases associated with ADHD across the lifespan: Fidgety Philipp and Pippi Longstocking at risk of multimorbidity?* Neurosci Biobehav Rev, 2022. **132**: p. 1157-1180.
7. Dalsgaard, S., et al., *Mortality in children, adolescents, and adults with attention deficit hyperactivity disorder: a nationwide cohort study.* Lancet, 2015. **385**(9983): p. 2190-6.
8. NICE. 2018; Available from: https://www.nice.org.uk/guidance/ng87.
9. CADDRA. 2018; Available from: https://www.caddra.ca/download-guidelines/
10. Boland, H., et al., *A literature review and meta-analysis on the effects of ADHD medications on functional outcomes.* J Psychiatr Res, 2020. **123**: p. 21-30.
11. Cortese, S., et al., *Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis.* Lancet Psychiatry, 2018. **5**(9): p. 727-738.
12. Mechler, K., et al., *Evidence-based pharmacological treatment options for ADHD in children and adolescents.* Pharmacol Ther, 2022. **230**: p. 107940.
13. Coghill, D., *Debate: Are Stimulant Medications for Attention-Deficit/Hyperactivity Disorder Effective in the Long Term? (For).* J Am Acad Child Adolesc Psychiatry, 2019. **58**(10): p. 938-939.
14. Swanson, J.M., *Debate: Are Stimulant Medications for Attention-Deficit/Hyperactivity Disorder Effective in the Long Term? (Against).* J Am Acad Child Adolesc Psychiatry, 2019. **58**(10): p. 936-938.
15. Osterberg, L. and T. Blaschke, *Adherence to medication.* N Engl J Med, 2005. **353**(5): p. 487-97.
16. Cramer, J.A., et al., *Medication compliance and persistence: terminology and definitions.* Value Health, 2008. **11**(1): p. 44-7.
17. Gajria, K., et al., *Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder - a systematic literature review.* Neuropsychiatr Dis Treat, 2014. **10**: p. 1543-69.
18. Buchanan, A., *A two-year prospective study of treatment compliance in patients with schizophrenia.* Psychol Med, 1992. **22**(3): p. 787-97.
19. Vrijens, B., et al., *A new taxonomy for describing and defining adherence to medications.* Br J Clin Pharmacol, 2012. **73**(5): p. 691-705.
20. Perwien, A., et al., *Stimulant treatment patterns and compliance in children and adults with newly treated attention-deficit/hyperactivity disorder.* J Manag Care Pharm, 2004. **10**(2): p. 122-9.

21. Ahmed, R. and P. Aslani, *Attention-deficit/hyperactivity disorder: an update on medication adherence and persistence in children, adolescents and adults.* Expert Rev Pharmacoecon Outcomes Res, 2013. **13**(6): p. 791-815.
22. Charach, A. and R. Fernandez, *Enhancing ADHD medication adherence: challenges and opportunities.* Curr Psychiatry Rep, 2013. **15**(7): p. 371.
23. Adler, L.D. and A.A. Nierenberg, *Review of medication adherence in children and adults with ADHD.* Postgrad Med, 2010. **122**(1): p. 184-91.
24. Atzori, P., et al., *Predictive factors for persistent use and compliance of immediate-release methylphenidate: a 36-month naturalistic study.* J Child Adolesc Psychopharmacol, 2009. **19**(6): p. 673-81.
25. Corkum, P., P. Rimer, and R. Schachar, *Parental knowledge of attention-deficit hyperactivity disorder and opinions of treatment options: impact on enrollment and adherence to a 12-month treatment trial.* Can J Psychiatry, 1999. **44**(10): p. 1043-8.
26. Yang, J., et al., *Adherence with electronic monitoring and symptoms in children with attention deficit hyperactivity disorder.* Psychiatry Investig, 2012. **9**(3): p. 263-8.
27. Weisman, O., et al., *Testing the Efficacy of a Smartphone Application in Improving Medication Adherence, Among Children with ADHD.* Isr J Psychiatry, 2018. **55**(2): p. 59-63.
28. Charach, A., et al., *Documenting adherence to psychostimulants in children with ADHD.* J Can Acad Child Adolesc Psychiatry, 2008. **17**(3): p. 131-6.
29. Emilsson, M., et al., *Beliefs regarding medication and side effects influence treatment adherence in adolescents with attention deficit hyperactivity disorder.* Eur Child Adolesc Psychiatry, 2017. **26**(5): p. 559-571.
30. Hodgkins, P., R. Sasané, and W.M. Meijer, *Pharmacologic treatment of attention-deficit/hyperactivity disorder in children: incidence, prevalence, and treatment patterns in the Netherlands.* Clin Ther, 2011. **33**(2): p. 188-203.
31. Christensen, L., et al., *Pharmacological treatment patterns among patients with attention-deficit/hyperactivity disorder: retrospective claims-based analysis of a managed care population.* Curr Med Res Opin, 2010. **26**(4): p. 977-89.
32. Marcus, S.C. and M. Durkin, *Stimulant adherence and academic performance in urban youth with attention-deficit/hyperactivity disorder.* J Am Acad Child Adolesc Psychiatry, 2011. **50**(5): p. 480-9.
33. Hébert, J., et al., *Adherence to psychostimulant medication in children with attention-deficit/hyperactivity disorder: the role of attitudes.* J Can Acad Child Adolesc Psychiatry, 2013. **22**(4): p. 317-23.
34. Ibrahim el, S.R., *Rates of adherence to pharmacological treatment among children and adolescents with attention deficit hyperactivity disorder.* Hum Psychopharmacol, 2002. **17**(5): p. 225-31.
35. Efron, D., et al., *Patterns of long-term ADHD medication use in Australian children.* Arch Dis Child, 2020. **105**(6): p. 593-597.
36. Lawson, K.A., et al., *Utilization patterns of stimulants in ADHD in the Medicaid population: a retrospective analysis of data from the Texas Medicaid program.* Clin Ther, 2012. **34**(4): p. 944-956.e4.
37. Lachaine, J., et al., *Treatment patterns, adherence, and persistence in ADHD: a Canadian perspective.* Postgrad Med, 2012. **124**(3): p. 139-48.
38. Antony, A., *Study of Factors Influencing Treatment Adherence in Childhood Attention Deficit Hyperactivity Disorder in a Tertiary Healthcare Facility.* Indian J Psychol Med, 2016. **38**(1): p. 20-4.
39. Pappadopulos, E., et al., *Medication adherence in the MTA: saliva methylphenidate samples versus parent report and mediating effect of concomitant behavioral treatment.* J Am Acad Child Adolesc Psychiatry, 2009. **48**(5): p. 501-510.

40. Hong, M., et al., *A 36 month naturalistic retrospective study of clinic-treated youth with attention-deficit/hyperactivity disorder.* J Child Adolesc Psychopharmacol, 2014. **24**(6): p. 341-6.
41. Sitholey, P., V. Agarwal, and S. Chamoli, *A preliminary study of factors affecting adherence to medication in clinic children with attention-deficit/hyperactivity disorder.* Indian J Psychiatry, 2011. **53**(1): p. 41-4.
42. Hong, M., et al., *Naturalistic Pharmacotherapy Compliance among Pediatric Patients with Attention Deficit/Hyperactivity Disorder: a Study Based on Three-Year Nationwide Data.* J Korean Med Sci, 2016. **31**(4): p. 611-6.
43. Hodgkins, P., et al., *Management of ADHD in children across Europe: patient demographics, physician characteristics and treatment patterns.* Eur J Pediatr, 2013. **172**(7): p. 895-906.
44. Bhang, S.Y., et al., *Factors that Affect the Adherence to ADHD Medications during a Treatment Continuation Period in Children and Adolescents: A Nationwide Retrospective Cohort Study Using Korean Health Insurance Data from 2007 to 2011.* Psychiatry Investig, 2017. **14**(2): p. 158-165.
45. Kiliç, B.G., et al., *[Sociodemographic and clinical factors associated with compliance to methylphenidate treatment in children with attention deficit hyperactivity disorder].* Turk Psikiyatri Derg, 2007. **18**(3): p. 207-13.
46. Thiruchelvam, D., A. Charach, and R.J. Schachar, *Moderators and mediators of long-term adherence to stimulant treatment in children with ADHD.* J Am Acad Child Adolesc Psychiatry, 2001. **40**(8): p. 922-8.
47. Cummings, J.R., et al., *Racial and Ethnic Differences in ADHD Treatment Quality Among Medicaid-Enrolled Youth.* Pediatrics, 2017. **139**(6).
48. Bai, G.N., et al., *Effectiveness of a focused, brief psychoeducation program for parents of ADHD children: improvement of medication adherence and symptoms.* Neuropsychiatr Dis Treat, 2015. **11**: p. 2721-35.
49. Ji, X., et al., *Racial-Ethnic Differences in Patterns of Discontinuous Medication Treatment Among Medicaid-Insured Youths With ADHD.* Psychiatr Serv, 2018. **69**(3): p. 322-331.
50. Wong, I.C., et al., *Cessation of attention deficit hyperactivity disorder drugs in the young (CADDY)--a pharmacoepidemiological and qualitative study.* Health Technol Assess, 2009. **13**(50): p. iii-iv, ix-xi, 1-120.
51. Bahmanyar, S., et al., *Pharmacological treatment and demographic characteristics of pediatric patients with Attention Deficit Hyperactivity Disorder, Sweden.* Eur Neuropsychopharmacol, 2013. **23**(12): p. 1732-8.
52. McCarthy, S., et al., *Attention-deficit hyperactivity disorder: treatment discontinuation in adolescents and young adults.* Br J Psychiatry, 2009. **194**(3): p. 273-7.
53. MTA_Cooperative_Group., *A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD.* Arch Gen Psychiatry, 1999. **56**(12): p. 1073-86.
54. MTA_Cooperative_Group., *Moderators and mediators of treatment response for children with attention-deficit/hyperactivity disorder: the Multimodal Treatment Study of children with Attention-deficit/hyperactivity disorder.* Arch Gen Psychiatry, 1999. **56**(12): p. 1088-96.
55. Fried, R., et al., *An innovative SMS intervention to improve adherence to stimulants in children with ADHD: Preliminary findings.* J Psychopharmacol, 2020. **34**(8): p. 883-890.
56. Biederman, J., et al., *Evidence of Low Adherence to Stimulant Medication Among Children and Youths With ADHD: An Electronic Health Records Study.* Psychiatr Serv, 2019. **70**(10): p. 874-880.
57. Gau, S.S., et al., *National survey of adherence, efficacy, and side effects of methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan.* J Clin Psychiatry, 2008. **69**(1): p. 131-40.
58. Palli, S.R., et al., *Persistence of stimulants in children and adolescents with attention-deficit/hyperactivity disorder.* J Child Adolesc Psychopharmacol, 2012. **22**(2): p. 139-48.

59. Marcus, S.C., et al., *Continuity of methylphenidate treatment for attention-deficit/hyperactivity disorder.* Arch Pediatr Adolesc Med, 2005. **159**(6): p. 572-8.
60. Chou, W.J., et al., *Better efficacy for the osmotic release oral system methylphenidate among poor adherents to immediate-release methylphenidate in the three ADHD subtypes.* Psychiatry Clin Neurosci, 2009. **63**(2): p. 167-75.
61. Rothenberger, A., et al., *An observational study of once-daily modified-release methylphenidate in ADHD: quality of life, satisfaction with treatment and adherence.* Eur Child Adolesc Psychiatry, 2011. **20 Suppl 2**(Suppl 2): p. S257-65.
62. Olfson, M., S. Marcus, and G. Wan, *Stimulant dosing for children with ADHD: a medical claims analysis.* J Am Acad Child Adolesc Psychiatry, 2009. **48**(1): p. 51-9.
63. Meyers, J., et al., *The impact of adjunctive guanfacine extended release on stimulant adherence in children/adolescents with attention-deficit/hyperactivity disorder.* J Comp Eff Res, 2017. **6**(2): p. 109-125.
64. Lambert, M.C., et al., *A Survival Analysis of Psychostimulant Prescriptions in New South Wales from 1990 to 2010.* J Child Adolesc Psychopharmacol, 2015. **25**(6): p. 475-81.
65. Gau, S.S., et al., *Determinants of adherence to methylphenidate and the impact of poor adherence on maternal and family measures.* J Child Adolesc Psychopharmacol, 2006. **16**(3): p. 286-97.
66. Faraone, S.V., J. Biederman, and B. Zimmerman, *An analysis of patient adherence to treatment during a 1-year, open-label study of OROS methylphenidate in children with ADHD.* J Atten Disord, 2007. **11**(2): p. 157-66.
67. Braun, S., et al., *Descriptive comparison of drug treatment-persistent, -nonpersistent, and nondrug treatment patients with newly diagnosed attention deficit/hyperactivity disorder in Germany.* Clin Ther, 2013. **35**(5): p. 673-85.
68. Tuncturk, M., et al., *Investigating the effects of age, IQ, dosing, and anthropometric measures on the treatment persistence in long-term methylphenidate use.* Nord J Psychiatry, 2023. **77**(4): p. 345-351.
69. Molife, C., et al., *Healthcare utilization and costs of children with attention deficit/hyperactivity disorder initiating atomoxetine versus extended-release guanfacine.* Curr Med Res Opin, 2018. **34**(4): p. 619-632.
70. Su, Y., et al., *Osmotic Release Oral System Methylphenidate Versus Atomoxetine for the Treatment of Attention-Deficit/Hyperactivity Disorder in Chinese Youth: 8-Week Comparative Efficacy and 1-Year Follow-Up.* J Child Adolesc Psychopharmacol, 2016. **26**(4): p. 362-71.
71. Wehmeier, P.M., R.W. Dittmann, and T. Banaschewski, *Treatment compliance or medication adherence in children and adolescents on ADHD medication in clinical practice: results from the COMPLY observational study.* Atten Defic Hyperact Disord, 2015. **7**(2): p. 165-74.
72. Raman, S.R., et al., *An observational study of pharmacological treatment in primary care of children with ADHD in the United kingdom.* Psychiatr Serv, 2015. **66**(6): p. 617-24.
73. Greven, P., et al., *Comparative treatment patterns, healthcare resource utilization and costs of atomoxetine and long-acting methylphenidate among children and adolescents with attention-deficit/hyperactivity disorder in Germany.* Eur J Health Econ, 2017. **18**(7): p. 893-904.
74. Brinkman, W.B., et al., *Relationship Between Attention-Deficit/Hyperactivity Disorder Care and Medication Continuity.* J Am Acad Child Adolesc Psychiatry, 2016. **55**(4): p. 289-94.
75. Johnston, C. and S. Fine, *Methods of evaluating methylphenidate in children with attention deficit hyperactivity disorder: acceptability, satisfaction, and compliance.* J Pediatr Psychol, 1993. **18**(6): p. 717-30.
76. Tzang, R.F., et al., *Naturalistic exploration of the effect of osmotic release oral system-methylphenidate on remission rate and functional improvement in Taiwanese children with attention-deficit-hyperactivity disorder.* Psychiatry Clin Neurosci, 2012. **66**(1): p. 53-63.

77. Bruno, C., et al., *Patterns of attention deficit hyperactivity disorder medicine use in the era of new non-stimulant medicines: A population-based study among Australian children and adults (2013-2020).* Aust N Z J Psychiatry, 2023. **57**(5): p. 675-685.
78. Miller, A.R., C.E. Lalonde, and K.M. McGrail, *Children's persistence with methylphenidate therapy: a population-based study.* Can J Psychiatry, 2004. **49**(11): p. 761-8.
79. Niemeyer, L., et al., *"When I Stop My Medication, Everything Goes Wrong": Content Analysis of Interviews with Adolescent Patients Treated with Psychotropic Medication.* J Child Adolesc Psychopharmacol, 2018. **28**(9): p. 655-662.
80. Kamimura-Nishimura, K.I., W.B. Brinkman, and T.E. Froehlich, *Strategies for improving ADHD medication adherence.* Curr Psychiatr, 2019. **18**(8): p. 25-38.
81. Khan, M.U. and P. Aslani, *A Review of Factors Influencing the Three Phases of Medication Adherence in People with Attention-Deficit/Hyperactivity Disorder.* J Child Adolesc Psychopharmacol, 2019. **29**(6): p. 398-418.
82. Charach, A., A. Ickowicz, and R. Schachar, *Stimulant treatment over five years: adherence, effectiveness, and adverse effects.* J Am Acad Child Adolesc Psychiatry, 2004. **43**(5): p. 559-67.
83. Leslie, L.K., et al., *Investigating ADHD treatment trajectories: listening to families' stories about medication use.* J Dev Behav Pediatr, 2007. **28**(3): p. 179-88.
84. Chen, C.Y., T. Gerhard, and A.G. Winterstein, *Determinants of initial pharmacological treatment for youths with attention-deficit/hyperactivity disorder.* J Child Adolesc Psychopharmacol, 2009. **19**(2): p. 187-95.
85. Chen, C.Y., et al., *Differential effects of predictors on methylphenidate initiation and discontinuation among young people with newly diagnosed attention-deficit/hyperactivity disorder.* J Child Adolesc Psychopharmacol, 2011. **21**(3): p. 265-73.
86. Baweja, R., C.A. Soutullo, and J.G. Waxmonsky, *Review of barriers and interventions to promote treatment engagement for pediatric attention deficit hyperactivity disorder care.* World J Psychiatry, 2021. **11**(12): p. 1206-1227.
87. Swanson, J.M., et al., *Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/hyperactivity disorder: symptom persistence, source discrepancy, and height suppression.* J Child Psychol Psychiatry, 2017. **58**(6): p. 663-678.
88. Sherman, M. and M. Hertzig, *Prescribing practices of ritalin: the Suffolk County, New York study.* Ritalin: Theory and patient management, 1991: p. 187-193.
89. Biederman, J., et al., *A naturalistic 10-year prospective study of height and weight in children with attention-deficit hyperactivity disorder grown up: sex and treatment effects.* J Pediatr, 2010. **157**(4): p. 635-40, 640.e1.
90. Pottegård, A., et al., *The use of medication against attention deficit hyperactivity disorder in Denmark: a drug use study from a national perspective.* Eur J Clin Pharmacol, 2012. **68**(10): p. 1443-50.
91. van den Ban, E., et al., *Less discontinuation of ADHD drug use since the availability of long-acting ADHD medication in children, adolescents and adults under the age of 45 years in the Netherlands.* Atten Defic Hyperact Disord, 2010. **2**(4): p. 213-20.
92. Zetterqvist, J., et al., *Stimulant and non-stimulant attention deficit/hyperactivity disorder drug use: total population study of trends and discontinuation patterns 2006-2009.* Acta Psychiatr Scand, 2013. **128**(1): p. 70-7.
93. Jensen, P.S., et al., *3-year follow-up of the NIMH MTA study.* J Am Acad Child Adolesc Psychiatry, 2007. **46**(8): p. 989-1002.
94. Chacko, A., et al., *Improving medication adherence in chronic pediatric health conditions: a focus on ADHD in youth.* Curr Pharm Des, 2010. **16**(22): p. 2416-23.
95. Zheng, X., et al., *Parent and Teacher Training Increases Medication Adherence for Primary School Children With Attention-Deficit/Hyperactivity Disorder.* Front Pediatr, 2020. **8**: p. 486353.

96. Ferrin, M., et al., *A Randomized Controlled Trial Evaluating the Efficacy of a Psychoeducation Program for Families of Children and Adolescents With ADHD in the United Kingdom: Results After a 6-Month Follow-Up.* J Atten Disord, 2020. **24**(5): p. 768-779.
97. Ferrin, M., et al., *Evaluation of a psychoeducation programme for parents of children and adolescents with ADHD: immediate and long-term effects using a blind randomized controlled trial.* Eur Child Adolesc Psychiatry, 2014. **23**(8): p. 637-47.
98. Montoya, A., F. Colom, and M. Ferrin, *Is psychoeducation for parents and teachers of children and adolescents with ADHD efficacious? A systematic literature review.* Eur Psychiatry, 2011. **26**(3): p. 166-75.
99. van Langen, M.J.M., et al., *Lost in explanation: internal conflicts in the discourse of ADHD psychoeducation.* BMC Psychiatry, 2022. **22**(1): p. 690.
100. Colom, F. and E. Vieta, *Psychoeducation Manual for Bipolar Disorder*. 2006, Cambridge: Cambridge University Press.
101. Hack, S. and B. Chow, *Pediatric psychotropic medication compliance: a literature review and research-based suggestions for improving treatment compliance.* J Child Adolesc Psychopharmacol, 2001. **11**(1): p. 59-67.
102. Lansky, S.B., et al., *Psychological correlates of compliance.* Am J Pediatr Hematol Oncol, 1983. **5**(1): p. 87-92.
103. Hoegy, D., et al., *Medication adherence in pediatric transplantation and assessment methods: a systematic review.* Patient Prefer Adherence, 2019. **13**: p. 705-719.
104. Gupta, S. and S. Bhatia, *Optimizing medication adherence in children with cancer.* Curr Opin Pediatr, 2017. **29**(1): p. 41-45.
105. Elhenawy, Y.I., et al., *Adherence to Insulin Therapy Among Children with Type 1 Diabetes: Reliability and Validity of the Arabic Version of the 4-Item Morisky Medication Adherence Scale.* Patient Prefer Adherence, 2022. **16**: p. 1415-1421.
106. Schwartz, D.D., et al., *Early risk factors for nonadherence in pediatric type 1 diabetes: a review of the recent literature.* Curr Diabetes Rev, 2010. **6**(3): p. 167-83.
107. Shah, R., et al., *Adherence to multiple medications in the TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) cohort: effect of additional medications on adherence to primary diabetes medication.* J Pediatr Endocrinol Metab, 2020. **33**(2): p. 191-198.
108. Capoccia, K., P.S. Odegard, and N. Letassy, *Medication Adherence With Diabetes Medication: A Systematic Review of the Literature.* Diabetes Educ, 2016. **42**(1): p. 34-71.
109. Currie, C.J., et al., *The impact of treatment non-compliance on mortality in people with type 1 diabetes.* J Diabetes Complications, 2013. **27**(3): p. 219-23.
110. Borus, J.S. and L. Laffel, *Adherence challenges in the management of type 1 diabetes in adolescents: prevention and intervention.* Curr Opin Pediatr, 2010. **22**(4): p. 405-11.
111. Wicker, E. and J.W. Cole, *Sudden Unexpected Death in Epilepsy (SUDEP): A Review of Risk Factors and Possible Interventions in Children.* J Pediatr Pharmacol Ther, 2021. **26**(6): p. 556-564.
112. Sveinsson, O., et al., *Pharmacologic treatment and SUDEP risk: A nationwide, population-based, case-control study.* Neurology, 2020. **95**(18): p. e2509-e2518.
113. Desai, M. and J.J. Oppenheimer, *Medication adherence in the asthmatic child and adolescent.* Curr Allergy Asthma Rep, 2011. **11**(6): p. 454-64.
114. Kaplan, A. and D. Price, *Treatment Adherence in Adolescents with Asthma.* J Asthma Allergy, 2020. **13**: p. 39-49.
115. Herrera, A.M. and D.A. Fitzgerald, *Question 1: Why do children still die from asthma?* Paediatr Respir Rev, 2018. **27**: p. 40-43.
116. Faraone, S.V., et al., *The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder.* Neuroscience & Biobehavioral Reviews, 2021. **128**: p. 789-818.

117. Matthijssen, A.M., et al., *Continued Benefits of Methylphenidate in ADHD After 2 Years in Clinical Practice: A Randomized Placebo-Controlled Discontinuation Study.* Am J Psychiatry, 2019. **176**(9): p. 754-762.
118. Lam, W.Y. and P. Fresco, *Medication Adherence Measures: An Overview.* Biomed Res Int, 2015. **2015**: p. 217047.
119. Parkin, R., F.M. Nicholas, and J.C. Hayden, *A systematic review of interventions to enhance adherence and persistence with ADHD pharmacotherapy.* J Psychiatr Res, 2022. **152**: p. 201-218.