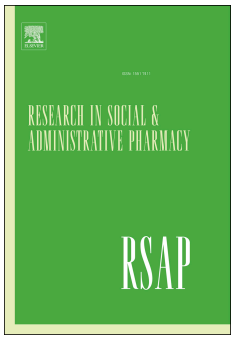

The impact of digital interventions on medication adherence in paediatric populations with attention deficit hyperactivity disorder, depression, and/or anxiety: A rapid systematic review and meta-analysis

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Title: The impact of digital interventions on medication adherence in paediatric populations with attention deficit hyperactivity disorder, depression, and/or anxiety: a rapid systematic review and meta-analysis

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The impact of digital interventions on medication adherence in paediatric populations with attention deficit hyperactivity disorder, depression, and/or anxiety: a rapid systematic review and meta-analysis

Abstract

Background

The growing prevalence of mental health disorders in children and adolescents coupled with poor medication adherence in the paediatric population is a major problem within healthcare systems affecting patient outcomes. Digital health interventions (DHIs) are primed to optimise medication adherence given the expansion of digital health markets and the increased usage of digital technologies by children and adolescents.

Objective

This rapid systematic review evaluates the impact of DHIs on optimising medication adherence amongst children and adolescents with mental health disorders compared to treatment as usual (TAU).

Methods

A rapid systematic search in electronic databases CINAHL Plus, Cochrane Library, MEDLINE, PubMed, and Scopus was conducted. The scope of the rapid systematic search included randomised controlled trials and quasi-experimental studies (non-randomised controlled trials) evaluating DHIs optimising medication adherence in children and adolescents with attention deficit hyperactivity disorder (ADHD), depression and/or anxiety. Meta-analyses were

conducted based on estimating pooled odds ratio (OR) and mean difference (MD) with 95% confidence interval using a random-effects model. Thematic analysis identified key avenues DHIs offer to optimise medication adherence.

Results

Four studies were found, with 502 participants included in the meta-analysis. An improvement in medication adherence was observed following DHIs for studies measuring dichotomous and continuous outcomes. However, the effect was not significant for the former. DHIs were shown to help bridge the gaps between patients and healthcare professionals, allowing for more frequent monitoring, communication, and assessments.

Conclusions

Medication adherence amongst children and adolescents with acute or chronic ADHD, anxiety or depression may be positively impacted by DHIs, but better-powered studies with a lower risk of bias are necessary. The evidence currently remains inconclusive on DHIs improving medication adherence in children and adolescents.

Keywords

Pediatrics, Mental Health, eHealth, Telemedicine, Medication Adherence, Systematic Review

Introduction

The turn of the 21st century has witnessed a remarkable surge in the populace using digital devices among people of all age groups, but most notably by children and adolescents owning smartphones, computerised devices or other digital technologies.[1,2] This period has also borne witness to a six-fold increase in the prevalence of mental health conditions in both children (2-12 years) and adolescents (13-18 years) including attention deficit hyperactivity disorder (ADHD), depression and anxiety, with Pitchforth et al.[3] reporting a rise from 0.8% in 1995 to 4.8% in 2014 in the United Kingdom (UK). Mental health illnesses impair the quality of life (QoL) of children and adolescents severely, with Richards et al.[4] stating that failure to successfully intervene results in greater suicide risks, self-harm, and substance misuse.

Attention-deficit hyperactivity disorder (ADHD) is a childhood heterogenous neurodevelopment disorder[5], with Thomas et al.[6] reporting that it affects 7.2% of people under 18 years of age worldwide. Depression is a complex, life-threatening mental disorder, characterised by a sense of unworthiness, sadness, feelings of guilt and suicidal thoughts. Jane Costello, Erkanli, and Angelo estimated the global prevalence of depression in adolescents to be 5.6%.[7] Anxiety is a fight-flight automatic neurophysiological response stimulated by imminent or perceived danger.[8] The treatment for these mental health conditions commonly involves behavioural therapy and/or pharmacotherapy in line with clinical evidence. However, some prescribed drugs can lead to poor tolerability, which is aggravated in children and adolescents, culminating in reduced medication adherence or discontinued therapy.[9,10]

The World Health Organization (WHO) defines eHealth as the “cost-effective and secure use of information and communications technologies (ICTs) in support of health and health-related

fields" which encompasses all forms of DHIs.[11,12] Telehealth refers to the use of ICTs to support long-distance clinical health care, patient education, and health administration via both remote clinical and non-clinical service delivery, whereas telemedicine refers only to remote clinical services.[12] Finally, telemental health is defined as the delivery of strictly mental health care services using ICTs such as video conferencing telephone, email or text messaging.[13]

Medication adherence is defined as "the extent to which the patient's action matches the agreed recommendations", i.e., the recommendations by the health care provider.[14] Intentional nonadherence is a lack of willingness from patients to take their medication, arising from personal preferences and attitudes, while nonintentional nonadherence is due to medication barriers such as difficulties in accessing treatment or failing to take ownership due to age or cognitive impairments.[14,15]

Nonadherence to psychotropic medication has been linked to the clinical worsening of psychiatric disorders in the paediatric population. Hamrin, McCarthy, and Tyson determined that poor medication adherence to psychotropic medicines in children is associated with adverse clinical and social outcomes including worsening psychiatric symptoms, increased strain on the family, and suicide.[16]

Nonadherence rates in children and adolescents with mental health conditions have been reported to be as high as 34.1%.[17] Patient barriers to medication adherence include forgetfulness, emotional factors and a lack of information[18] which are magnified in children and adolescents who are less likely to take ownership of their care compared to adult patients.[19] Medication adherence is particularly difficult in ADHD, with Adler and Nierenberg[20] reporting that associated difficulties with poor planning, impulsiveness and disorganisation make adherence especially challenging. Combining these difficulties with other barriers including potential

parent(s)'s lack of understanding, concerns with drug medication, and the fear of adverse effects[21] may also make planning treatment routines extremely difficult.

Moore, Powell, and Kyle[22] reported recent trends showing the importance of healthcare providers in managing mental health support schemes via close monitoring, conveying educational information and addressing patient concerns; measures which were shown to greatly improve medication adherence by Bingham et al.[23] These schemes would also include delivering text messages, reminders, apps and websites that collectively aim to improve patient education, dosing schedules, and communication; measures which present a compelling argument for the merit of digital tools in improving patient outcomes.[18]

Utilising digital technologies and platforms to enhance access and support treatment strategies should effectively improve medication adherence and reduce the severity of mental health disorders.[24,25] It is noteworthy that the use of digital health tools by children with mental health illnesses is well evidenced with Liverpool et al.[26] assessing the engagement of children and young people with DHIs and reporting an average retention rate of 79% in using an assortment of DHIs, with children and adolescents preferring those that offered more personalisation options, seamless connectivity with others, and video features.

While the evidence is abundant on the prevalent use of digital tools in paediatric populations, there is still a glaring gap in reported lines of investigation in literature synthesising and evaluating the evidence on the role of these digital interventions in improving medication adherence and patient outcomes in children and adolescents with ADHD, depression and/or anxiety.

The objective of this rapid systematic review was to synthesise and evaluate the published evidence which investigates the effect of digital interventions on optimising medication adherence in children and adolescents with ADHD, depression and/or anxiety compared to treatment as usual (TAU).

Methods

Methods for conducting the rapid systematic review including data collection and synthesis were outlined in the PROSPERO protocol (ID No. CRD42020210715). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines were used in conducting this rapid systematic review.[27] The research question was guided by the Population, Intervention, Comparison, and Outcome (PICO) framework.

Eligibility criteria

The rapid systematic review incorporated randomised controlled trials (RCTs) and quasi-experimental studies (non-randomised controlled trials) which investigated the impact of DHIs on optimising medication adherence in children and adolescents with ADHD, depression and/or anxiety. The comparator was TAU. No studies were excluded based on the study location or language, with international studies being considered and foreign papers being translated into English via Google Translate. Inclusion and exclusion criteria are found in Table 1.

Table 1. Inclusion and exclusion criteria.

Inclusion criteria:	Exclusion criteria:
• Children (2-12 years of age) and adolescents (13-18 years of age) who have been prescribed medication which is administered by a parent/guardian/caregiver or self-administered. • Patients diagnosed with acute or chronic ADHD, depression, and/or anxiety. • Studies that measured medication adherence either directly (e.g., drug plasma concentration) or indirectly (e.g., questionnaires). • Patients on medication to treat and/or prevent ADHD, depression and/or anxiety.	• Adults (aged 19 years and above) or those that were not diagnosed with acute or chronic ADHD, depression and/or anxiety. Infants (i.e., those below 2 years of age) were also excluded. • Children and adolescents who were not prescribed medication. • Comorbidities that lie outside psychiatric health

Types of digital intervention

DHIs included any electronic health (eHealth) intervention with medication adherence measured directly and/or indirectly. Other digital modes of delivery include text message reminders, smartphone applications, cyberspace websites, interactive digital media, telephone calls, and video consultations.

Primary outcome

Change in medication adherence following a minimum monthly duration, measured at the end of the treatment intervention/non-intervention. The minimum monthly duration was selected to evaluate the short-term impact and long-term expectations on medication adherence effectively. Measurements of medication adherence included direct and indirect measures. These included pill counts, patient report, medication usage questionnaires, review of prescription/ dispensing/ collection records, electronic monitoring systems, structured interviews, and therapeutic drug monitoring. A broad collection of measures was accepted as there is no universal approach to measuring medication adherence according to the literature.[28] Medication adherence to multiple medicines (≥2 concomitant medicines) as well as monotherapy were considered.

Search strategy

An unblinded rapid systematic search was performed for primary studies within the following electronic databases: CINAHL Plus, Cochrane Library, MEDLINE, PubMed, and Scopus. International studies from January 2000 until November 2020 were included. Rapid systematic reviews incorporate key features of a standard systematic review but simplify conventional review methods (i.e., search strategies) in addressing time constraints.[29]

Medical Subject Headings (MeSH) and text words considering synonyms were used in developing the full search strategy (Table 2). Because this study was designed as a rapid systematic review, the number of screened records was capped to ≤2000 per database utilising the search filters found on each database, with the produced results being sorted by best match/relevancy. A grey literature search in Google Scholar was performed screening the first 200 hits by entering the search term combination (Table 2).

A manual search was performed by reviewing the citation lists of relevant systematic reviews and meta-analyses and identifying suitable studies found on Google Scholar using the search term combination (Table 2). A forward citation search was also conducted. An updated search was carried out on September 8th, 2021. The reference management software Mendeley[30] was used for data storage, with identified records uploaded and duplicates removed. The number of studies excluded as well as the reasons for exclusion when screened by title, abstract and full-text articles was also documented.

Table 2. Search term combination used in the search strategy. Medical Subject Headings (MeSH) are highlighted in bold.

Domain 1 (Population)	Domain 2 (Disease state)	Domain 3 (Study location)	Domain 4 (Digital intervention)	Domain 5 (Patient outcome)	Domain 6 (Study design)
Child, Preschool OR **Child** OR Children OR Kid OR Teen OR Youngster OR Adolesc OR Paediatric OR Pediatric	AND Attention deficit hyperactivity disorder OR ADHD OR **Attention Deficit Disorder with Hyperactivity** OR ADDH AND **Anxiety** AND **Depression**	AND Pharma OR Drugstore OR **General Practice** OR Hospital	AND **Medical informatics** OR Clinical Informatics OR Computer Science, Medical OR Health Informatics OR Health Information Technology OR Health Information Technologies OR Informatics, Clinical OR Informatics, Medical OR Information Science, Medical OR Medical Computer Science OR Medical Information Science OR **Telemedicine** OR Telehealth OR Tele-health OR Telecare OR Tele-care OR Digital OR mHealth OR Mobile Health OR m-health OR m health OR eHealth OR ehealth OR e health OR Virtual OR **Internet** OR Cyber Space OR Cyberspace OR World Wide Web OR **Online Systems** OR On-Line Systems OR **Patient Portals** OR Patient Internet Portals OR Patient Portal OR Patient Web Portal OR Patient Web Portals OR Browser OR **Communications Media** OR **Multimedia** OR Interactive Media OR Interactive Voice Response OR **Social Media** OR **Reminder Systems** OR Electronic OR Monitor OR Device OR Wearable OR Alert OR **Computers** OR **Computers, Handheld** OR Tablet Computers OR **Cell Phone** OR Cellular phone OR Mobile Phone OR Mobile Telephone OR **Smartphone** OR Smart Phone OR Smart Phones OR **Mobile Applications** OR Mobile Apps OR Apps OR **Text Messaging** OR Short Message Service OR Text Messages OR Texting OR **Video Games** OR Computer Games OR **Gamification** OR **MP3-Player** OR Automated OR **Automation**	AND **Medication Adherence** OR Medicines Adherence OR Medication Compliance OR Medicines Compliance OR Medication Non-Adherence OR Medicines Non-Adherence OR Medication Non-Compliance OR Medicines Non-Compliance OR Medication Nonadherence OR Medicines Nonadherence OR Medication Noncompliance OR Medicines Noncompliance OR Medication Persistence OR Drug Adherence OR Drug Compliance OR Drug Non-Adherence OR Drug Non-Compliance OR Drug Nonadherence OR Drug Noncompliance OR Drug Persistence OR Patient Adherence OR **Patient Compliance** OR Patient Non-Adherence OR Patient Non-Compliance OR Patient Nonadherence OR Patient Noncompliance OR Patient Persistence OR **Drug Therapy** OR Pharmacotherapy	AND **Randomized Controlled Trial** OR Non-Randomized Controlled Trials OR Quasi-Experimental Studies OR **Clinical Trial** OR Clinical Trials

Data extraction

A data extraction form was developed (based on Cochrane Effective Practice and Organisation of Care (EPOC) Resources for review authors)[31] and pilot tested on 5 randomly selected studies. The following information was extracted from the included studies: participants (number of participants, age, gender, setting, and region(s)/country/countries where the study was undertaken), interventions (mode of digital delivery (will be coded), timing, frequency, and length), comparators (definition of the comparator, timing, frequency, and length), outcomes (how medication adherence was measured (self-report and/or objective), medication adherence scores, and timing of measurements), and study design. Data on each DHI was extracted and all measures of medication adherence were incorporated, with the final recorded measurement used if different measurements were taken at multiple timepoints post-intervention. Data were extracted independently by two reviewers. The title/abstract was screened first followed by full-text screening to determine eligibility (by two reviewers). Contact details were extracted from the full-text article and further study information was requested from authors via email or phone, when necessary, with a maximum of two attempts made to contact authors. Any disagreements in the data extraction were resolved by reaching a consensus through discussion between the two reviewers. Criteria for generating funnel plots to check for publication bias was a minimum of 10 studies included, with funnel plot asymmetry tested statistically.

Risk of bias in individual studies

The validity of individual studies included in the review was assessed using the revised Cochrane Risk-of-Bias (RoB 2) tool for randomised controlled trials and the Risk of Bias in Non-

Randomised Studies - of Interventions (ROBINS-I) tool for non-randomised controlled trials.[32] Assessing the risk of bias in included studies was conducted at the outcome level. The risk of bias of each study was compiled and presented using the robvis visualisation tool.[33] The risk of bias for each study was reviewed by two reviewers, with any disagreements resolved by reaching a consensus through discussion between the two reviewers.

Synthesis of results

The principal summary measures were the mean difference in the levels of adherence from the intervention group in comparison to the control group for continuous outcomes (post-intervention) with a 95% confidence interval using a random-effects model, standard deviations were also recorded. For dichotomous outcomes, effect measures were calculated as odds ratios with a 95% confidence interval using a random-effects model. The continuous and dichotomous outcomes were presented separately. Review Manager 5.4 (RevMan) was used to prepare the meta-analysis and create Forest plots displaying both result outcomes by combining the included studies.[34] RevMan generates forest plots of dichotomous and continuous outcomes separately. Heterogeneity and consistency were measured using the I^2 statistic for each meta-analysis.

A thematic analysis of the included studies was derived following Braun and Clarke[35] six-phase framework to identify patterns or themes within qualitative data. This was performed utilising an inductive approach to ensure the themes generated were strongly linked to the data, as opposed to being guided by pre-existing theories. The two reviewers familiarised themselves with the content of the data within all sections of the full-text papers and interpreted both the overt and implicit meanings. Each extract was adjoined to a descriptive term (i.e., codes) which allowed

for the data to be systematically organised and for patterns within the text to be identified. The produced codes were then combined to generate themes, with vague or irrelevant codes removed from the thematic coding process. Themes were then reviewed in assessing whether they accurately represented the data found and then collated to produce meta-themes which underpinned central concepts in line with the research question. Any disagreements were resolved by reaching a consensus through discussion between the two reviewers.

Results

Study selection

The number of identified records from the principal databases was 598,650, with an additional 33 records identified through other sources. The total number of screened records was 14,545 once duplicates had been removed. Of the records that were screened, a total of 295 studies were excluded for failing to meet the inclusion criteria, and a further 88 studies excluded as the full-text articles were unavailable. Authors were contacted at least twice for full-text articles and/or additional study information. The study was excluded if the data extracted was not sufficient to be considered as part of the core inclusion criteria.

Adjusting for records excluded, 387 full-text articles were assessed for eligibility, with 4 studies included in the qualitative and quantitative syntheses. A PRISMA flow diagram of the study selection is displayed in Figure 1. The updated search produced no additional studies meeting the eligibility criteria.

Figure 1. PRISMA flow diagram of study selection. *The number of records screened in each database was capped to ≤2000 records.

Study Characteristics

Methods

Of the four included studies, two were randomised controlled trials and two were quasi-experimental trials, with all selected studies published in English. All studies had a follow-up period of at least 30 days to assess the primary outcome of medication adherence and a minimum duration of 5 weeks. None of the studies included a pre-intervention or baseline measurement of medication adherence for both the intervention and control groups. A summary of the study characteristics is found in Table 3.

Participants

The included studies involved 502 participants. The mean age of participants was 9.79 years. The proportion of males was 68.53% (344/502). Based on the number of included participants, ADHD was the most prevalent mental health condition (91.43%), followed by anxiety (1.39%), then depression (1.39%), in addition to associated disorder subtypes (5.25%).

Intervention

The conducted interventions were digitally based, promoting communication and patient independence, and aiming to optimise the participant's medication adherence. These include SMS text messages sent daily to the participant's mobile phones to remind them of the medication dose in Fried et al.[36], mobile applications downloaded onto the participant's phone which achieved the same feat in Weisman et al.[37]. Telemental health services were also employed in a study that had clinical appointments held online for counselling[38], with the final study conducting computerised, digital tests to assess medication adherence (QbTest).[39]

Comparator

The comparator interventions were non-intervention groups, with participants following treatment as usual (TAU) without any other variables changed so that only the impact of DHIs on medication adherence could be assessed. Digital interventions were deployed as an adjunct to treatment as usual in intervention groups, and except for one included study[36], all studies incorporated patients on monotherapy alone.

Outcomes

In all studies, the primary outcome was medication adherence to stimulants, antidepressants or anxiolytic medications post-intervention following a form of DHIs. Medication adherence was measured using either pill counts, parent-entered logs on mobile applications, and/or prescription refills. These adherence measurement tools were validated before commencing the study. Measurements of medication adherence in the included studies were all direct, except for one

277 study that used indirect (parent-report) measures.[36] A summary of the included studies is found
278 in Table 3.

279 **Table 3.** Summary of study characteristics.

Study	Sample size (n) and study design	Region	Age range (mean) and gender	The target of digital intervention	Digital intervention	n	Frequency	Comparator intervention	n	Frequency	Medication adherence measurement
Weisman et al. 2018	39 RCT	Israel	9.56 ± 2.41 years 27 M 12 F	Children 3-12 years old diagnosed with ADHD following a diagnostic interview conducted by a qualified child and adolescent psychiatrist.	iCON mobile application functions as a medication reminder with prompts to take medication occurring at 7 am every morning	19	Reminders sent at 7 am every morning through the mobile app Patient questionnaires could be completed at any time	Control group, TAU	20	N/A	Pill count
Williams 2020	86 nRCT	United States of America	12.78 ± 4.22 years 33 M 53 F	Children and adolescents aged 6-17 years with one or more of the following mental health illnesses; anxiety, adjustment disorder, disruptive behaviour, defiant behaviour, neurocognitive disorder, and ADHD	Appointments made with mental health counsellors digitally, Telemental health service	43	Frequency and timing not mentioned	Control group, TAU	43	Same as the intervention group	Prescription refill

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Study	Sample size (n) and study design	Region	Age range (mean) and gender	The target of digital intervention	Digital intervention	n	Frequency	Comparator intervention	n	Frequency	Medication adherence measurement
Fried et al. 2020	333 nRCT	The United States of America, & Norway	9.13 ± 2.0 years 245 M 88 F	Children with ICD-10 or DSM-5 ADHD, 6–12 years of age starting ADHD stimulant medication	SMS text message reminders for medication adherence to stimulant medication	87	Text messages reminders were sent and received once daily	Control group, TAU	246	N/A	Prescription refill
Williams et al. 2021	44 RCT	United Kingdom	9.25 ± 2.49 years 39 M 5 F	Children and adolescents (6-17 years), with a clinical diagnosis of ADHD, commencing stimulant medication therapy	A digital assessment, the Quantified Behaviour (Qb) Test, for medication management	21	QbTest completed once at baseline and two follow-up QbTests at 2-4 weeks and 8-10 weeks	Control group, TAU	23	Same as the intervention group	Parent report

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Risk of bias within studies

A summary of the risk of bias analysis is shown in Figures 2 and 3. Overall, all studies contained some concerns over the degree of bias, unpredictable over whether the bias would lean heavily toward the intervention or comparator group. The absence of blinding to participants, providers or healthcare professionals was the most common source of bias. The second was that the primary outcome measure could have been influenced by knowledge of the intervention received. However, data for outcomes were available for all, or nearly all the participants randomised in all studies. Methods of measuring medication adherence were appropriate, although they varied from pill counts, parent-entered medication logs, and prescription refills. Studies were not free from baseline differences in gender, with most trials recruiting boys over girls for both intervention and comparator groups. Outcomes and effects were generally not selectively reported based on the results, except for one study.[38]

Figure 2. Summary of the risk of bias for randomized controlled trials.

Figure 3. Summary of the risk of bias for non-randomized controlled trials.

Synthesis of results

The results of each meta-analysis, including confidence intervals and measures of consistency, are displayed in Figure 4 for studies evaluating dichotomous outcomes and Figure 5 for studies evaluating continuous outcomes. Medication adherence data were available for all 4 studies, with 547 patients participating but only 502 reporting results for data synthesis. Studies presenting

dichotomous outcomes showed an improvement in medication adherence following patient participation with the DHIs (odds ratio 2.30, 95% confidence interval [0.84, 6.33]). However, the analysis demonstrated that the effect was not significant ($p = 0.11$). An improvement in medication adherence was also shown in studies measuring continuous outcomes (mean difference 0.15, 95% confidence interval [0.01, 0.29], $p < 0.05$). For studies measuring dichotomous outcomes, there was substantial heterogeneity ($I^2 = 58\%$; $X^2 = 2.38$, df = 1; P = 0.12). While heterogeneity was minimal for studies measuring continuous outcomes ($I^2 = 3\%$; $X^2 = 1.03$, df = 1; P = 0.31).

A qualitative appraisal suggested low levels of heterogeneity concerning the pooled results. Across the included studies, sociodemographic characteristics were homogeneous, with the range of children and adolescent participants between 9-14 years of age. All the outcome measures used from the 4 included studies were direct except for one which relied on parent reports.[39] Timepoints at which results were measured were over 5-12 weeks. Comparator groups for all included studies were treatment as usual/no intervention. Studies typically matched the intervention and comparator groups for age, sex, socioeconomic status, and type of medication (particularly for ADHD) utilising a propensity score. All four studies included participants with a diagnosis of ADHD.

Figure 4. Forest plot of studies evaluating digital interventions to optimise medication adherence against comparators for dichotomous outcomes.

Figure 5. Forest plot of studies evaluating digital interventions to optimise medication adherence against comparators for continuous outcomes.

Qualitative synthesis

Table 4. Summary of themes and meta-themes that emerged from thematic analysis.

Extract	Codes	Theme description	Analytical theme (Meta-theme)
• "Parents had no reservations about completing questionnaires and found them useful in highlighting areas of improvement or change." [39] • "Allowing for more frequent communications as well as better monitoring of adherence to the prescribed treatment." [37] • "'I think it has been good to have that support. Because in the past, we have had an appointment and then not been seen for months and months.'" [39] • "While the Qbtest is both an aid to communication, it is also a powerful additional 'voice' in the discussion." [39] • "QbTest was described by both groups (parents and clinicians) as increasing their confidence in the child's treatment" [39] • In non-intervention groups "it was claimed that most children with ADHD had no contact with their physician during the first month of medication treatment." [37]	Communication Optimism Openness Benefits Attitudes Collaboration Adherence Discussion Improvement Opportunities	1. Caregivers' acceptability of DHIs 2. Impact on service delivery 3. Overcoming barriers to treatment 4. Greater opportunities for patients to contact clinicians	Bridging the gap between child, parent/s, and healthcare professionals

Thematic analysis led to the identification of the following theme:

- Bridging the gap between child, parent/s, and healthcare professionals

DHIs allowed for more frequent monitoring, communication and patient assessment promoting medication adherence. There were increased opportunities for consultation enforcing the patients' education on medication treatment. Also, there was a lack of contact between children

and healthcare professionals during the initial month of medication treatment in non-intervention groups, correlating with lower adherence rates.

Discussion

Overall, the evidence demonstrated that DHIs including SMS text messages, telemental health, and mobile app features impact medication adherence positively. Improvements in medication adherence were substantial in studies utilising mobile phone medication reminders[36] but minimal in telemental health[38] and digitalised evaluation tests[39].

Two of the included studies[36,37] evaluating the impact of SMS text and mobile health app reminders on medication adherence reported the greatest improvement in medication adherence in the intervention group compared to the control. This implies that smartphone reminders are superior at optimising medication adherence in children and adolescents compared to video counselling, telephone calls and digitalised evaluation tests. This could be attributed to the prevalence of problematic smartphone usage (i.e., the inability to regulate use) estimated to be around 23.3% in children and young people[41] and associated with an increased prevalence of anxiety and depression. Children and adolescents with anxiety and/or depression are more likely to have increased daily usage of mobile phones and are better equipped at acknowledging reminders and improving their medication adherence. A systematic review conducted by Grist et al.[42] supports these claims by demonstrating acceptability and increased usage of mobile health apps amongst children and adolescents with mental health disorders.

The present review found inconclusive results relating to the impact of telehealth on medication adherence. There is a lack of comparative studies on mental health conditions validating these

findings. It cannot be determined whether telehealth interventions should be incentivised over other forms of DHIs. Poor acceptability of telehealth interventions could be attributed to technical difficulties and lengthy intervention durations. Alternatively, greater flexibility in the timings of digital appointments could have yielded greater acceptability.

Most patients (97.81%) completed the trials successfully which reflects the high engagement of participants with digital technologies and their willingness to communicate with healthcare professionals. The increased engagement is further supported by the findings of the study conducted by Liverpool et al.[26] demonstrating that most patients comply with DHIs. Although the present review failed to determine which DHIs patients preferred, a survey conducted by Jenssen et al.[40] found that of 3336 participants, 75.5% were happy communicating with their provider via phone calls, 13.3% via text messaging and 3.1% using social media.

There was a difference in effect when comparing studies with dichotomous and continuous outcomes. This could be attributed to one study[39] measuring dichotomous outcomes using self-reports of medication adherence. Al-Hassany et al.[28] determined that children and adolescents with ADHD might unintentionally provide inaccurate information in self-reports. Contrastingly, other studies[36,38] measured continuous outcomes using direct means (e.g., prescription refills).

From the included studies, increasing the number and frequency at which DHIs were delivered correlated with an improvement in medication adherence. Two studies delivered the DHI daily[36,37], resulting in a higher proportion of participants taking their medication as instructed by up to 23% compared to the control. This suggests that increasing the frequency and rate at which DHIs are provided might also lead to improving medication adherence. This could be attributed to providing patients with ample opportunities to assess their treatment, whilst also strengthening their understanding of medication management. However, increasing the frequency would

require increased healthcare resources, including costs and heavier healthcare provider workloads. So, striking a balance between the frequency at which a DHI is delivered, and the necessary dedicated resources is paramount when a decision is made to adopt this approach.

An important and unique consideration for medication adherence in children and adolescents includes the significant influence of primary caregivers (parents/carers/guardians) which decides the degree of success of any intervention. Caregivers play a pivotal role in paediatric health, working in their best interests to enhance parent-child relations and ensure the child adheres to dosing schedules. Parent-child interactions determine the degree of oppositional-defiant behaviour, with Dietz et al. finding that positive reinforcement and increased engagement from parents improve the wellbeing of children, which is particularly pertinent in the management of psychiatric disorders.[43]

Nagae et al. evaluated the attitudes towards medication in children (<14 years) compared to adolescents (≧ 14 years), as well as assessing degrees of trust between the parent(s) and child.[44] Adolescents' attitudes towards psychotropic medicines were found to be more positive compared to children and were strongly associated with better adherence. This was closely linked to the ability of older adolescents to communicate their awareness of the effects of medications, in addition to parents displaying increased trust and transferring management of treatment around early adolescence. For children, Nagae et al. suggested that interventions improving a mother's understanding of the importance of medication can subsequently improve child adherence.[44] The thematic analysis supports this, as it suggested that DHIs can increase the parents' confidence in the child's treatment, corresponding to improved medication adherence.

DHIs provide opportunities to mitigate unnecessary GP appointments, hospital admissions, and pharmacy visits for particularly vulnerable individuals.[45] Although sparse, the available evidence

suggests that medication adherence can be enhanced using digital technologies for mental health disorders, with extensive research being conducted for other clinical conditions. Brassel, Zhang, and Jofre-Bonet[46] proposed that digitalisation enables greater patient involvement and control over their healthcare via managing prescriptions and empowering practitioners to contact their patients more frequently via telehealth. The thematic analysis also suggested that DHIs could work as an adjunct to conventional measures, as it was demonstrated to increase the frequency of patient/clinician communication and allow for more accurate monitoring of treatment adherence.

Health inequalities are a major concern in the children and adolescent populations, with socioeconomic status, health-service barriers (e.g., no lack of healthcare providers in the local community), and parent-child relations contributing to the mediation or moderation of health inequalities.[47] The thematic analysis indicated that a lack of contact between patients and healthcare providers contributed to poorer health outcomes. Digital technologies may reduce health inequalities by improving access to health information, reducing costs on frontline services, and providing opportunities for public healthcare services to consult inclusion health groups, protected groups and patients living in deprived areas.[48] For example, an evaluation of the NHS Widening Digital Participation Programme in the UK[48], which recruited people in excluded communities at risk of worse health outcomes, found that 51% of people receiving support used the internet to improve their psychological wellbeing and mental health, as well as 65% who felt more informed regarding their health. The findings from the thematic analysis further support this, suggesting that digital interventions are well-accepted, can improve attitudes towards pharmacological treatment, and overcome barriers to the delivery of care.

The present rapid systematic review reported combined data across four studies, two RCTs and two non-RCTs. The main limitation of this rapid systematic review was the high variation in

sample sizes and unequal representation of the psychiatric conditions at focus, namely ADHD, depression, and anxiety. Indeed, most participants were children and adolescents with a diagnosis of ADHD across all four studies, and only a single study[39] evaluated patients with anxiety and/or depression.

The small number of studies to pool in the present rapid systematic review resulted in an underpowered analysis. An example is failing to meet the criteria of producing an asymmetrical funnel plot to determine the publication bias due to the limited number of relevant studies for inclusion.

One study had elements that suggested a serious risk of bias[36], due to lack of blinding, randomisation, or concealment of allocation sequence, as well as baseline characteristic imbalances. This implies low confidence that the data represents an impact of the digital intervention on medication adherence.

Another limitation of this rapid systematic review was the pooling of data from a group of studies that evaluated the primary outcome using varying direct and indirect measures. The included studies applied different techniques in measuring medication adherence targeting patients with ADHD, depression and/or anxiety. The overreliance on self-report data without corroborating with objective measures in one study[39] may overestimate the impact of digital interventions due to participants' response bias towards success. This makes it increasingly difficult to assert medication adherence beyond prescription refills and pill count reports. Fried et al.[36] also defined medication adherence as a "timely" refill of the first prescription (within 37 days) which was determined from prescription dates documented in patients' electronic medical records. No data confirms whether patients indeed took the medication which contrasts with other included studies that measured patient recorded adherence.

Across the four studies, follow-up periods and trial duration were 6 weeks on average, failing to assess the long-term effects and sustainability of using digital interventions to improve medication adherence, except for two trials[37,39] that consisted of multiple follow-ups extending to 8-10 weeks and which suggested an insignificant medium-term improvement in medication adherence. Long-term research using a broader range of lengthier follow-up periods is required to evaluate the long-term effects of DHIs.

Two studies[36,37] failed to assess the participants' compliance/engagement with digital intervention and how this could impact adherence. It is recommended that future research continues to trial and report the impact of digital interventions on medication adherence, in addition to documenting engagement. Future research should also evaluate how different frequencies of the same digital intervention can influence medication adherence to determine the optimal delivery. Moreover, the increased usage of video games in children and adolescents[1] suggests opportunities for future research to conduct trials evaluating the impact of video games on medication adherence or other patient outcomes such as emotional wellbeing and quality of life in children with ADHD, depression and/or anxiety.

Conclusions

The present rapid systematic review indicates that DHIs may improve medication adherence amongst children and adolescents with acute or chronic ADHD, anxiety, or depression. There is evidence suggesting that DHIs should be designed to take advantage of mobile health applications already available in the digital market, considering the positive impact that mHealth

interventions had on medication adherence compared to TAU as well as other types of digital interventions.

Digital innovators could seize the opportunity to adapt existing mobile health apps and incorporate medication adherence reminders among other features that can collectively improve patient outcomes, including delivering online counselling and electronic patient satisfaction questionnaires.

The evidence that DHIs would improve medication adherence remains inconclusive considering the sparse evidence. Better powered studies with a lower risk of bias are necessary. This rapid systematic review highlighted some of the benefits that digital interventions may offer to optimise medication adherence and improve patient outcomes.

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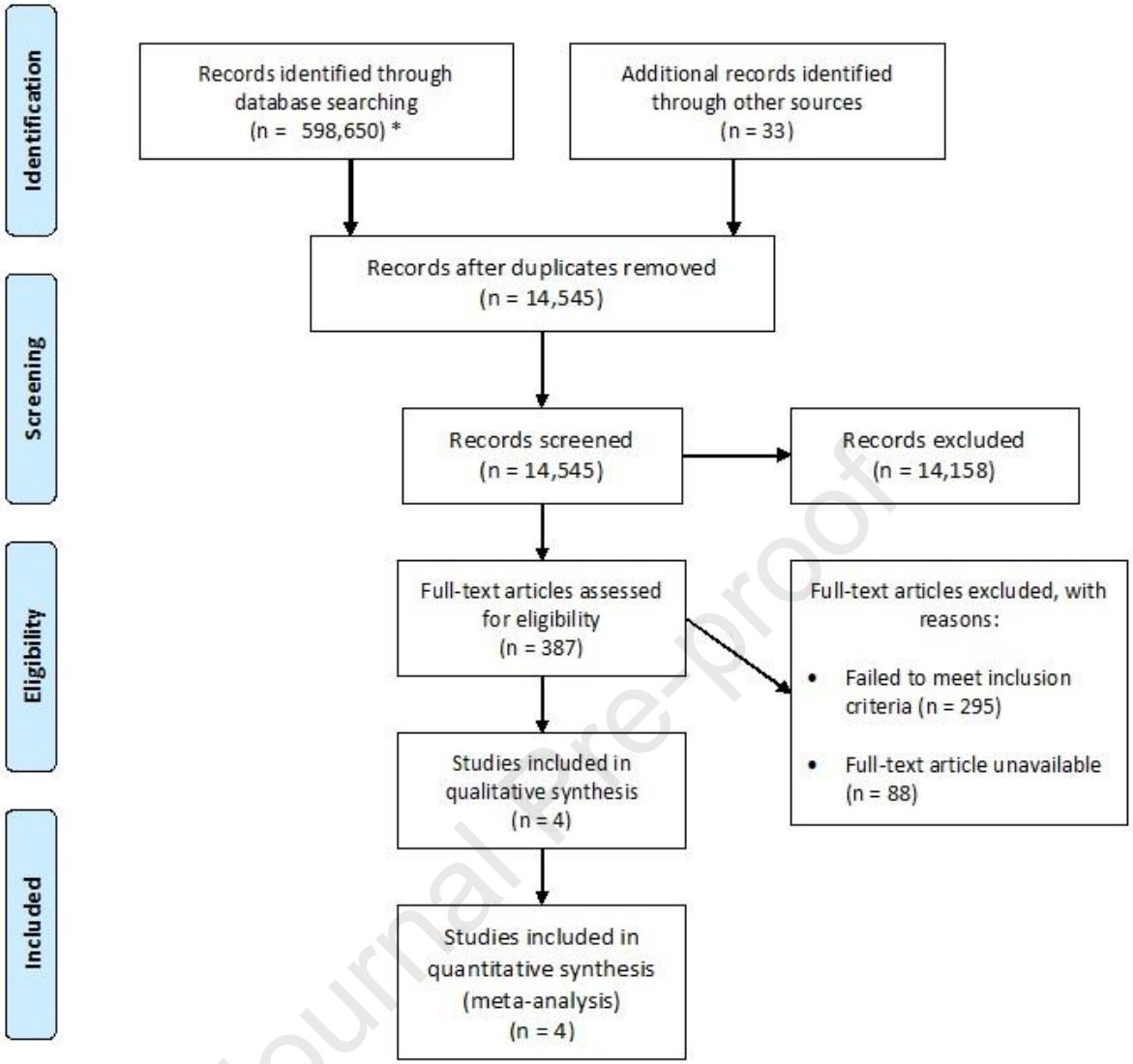
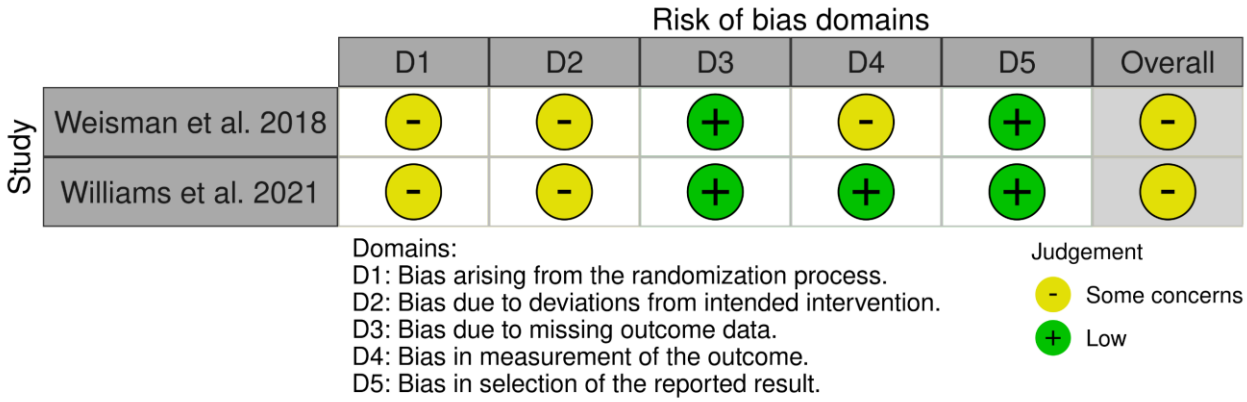
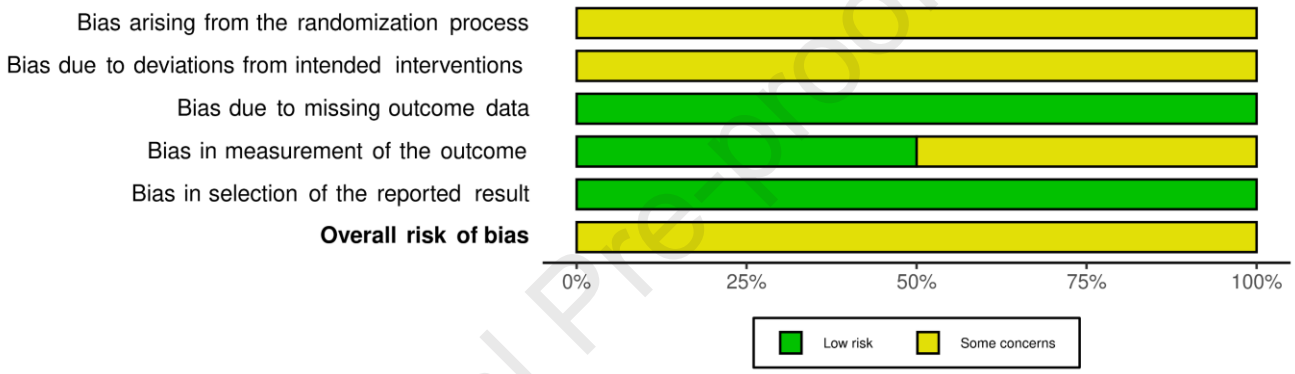
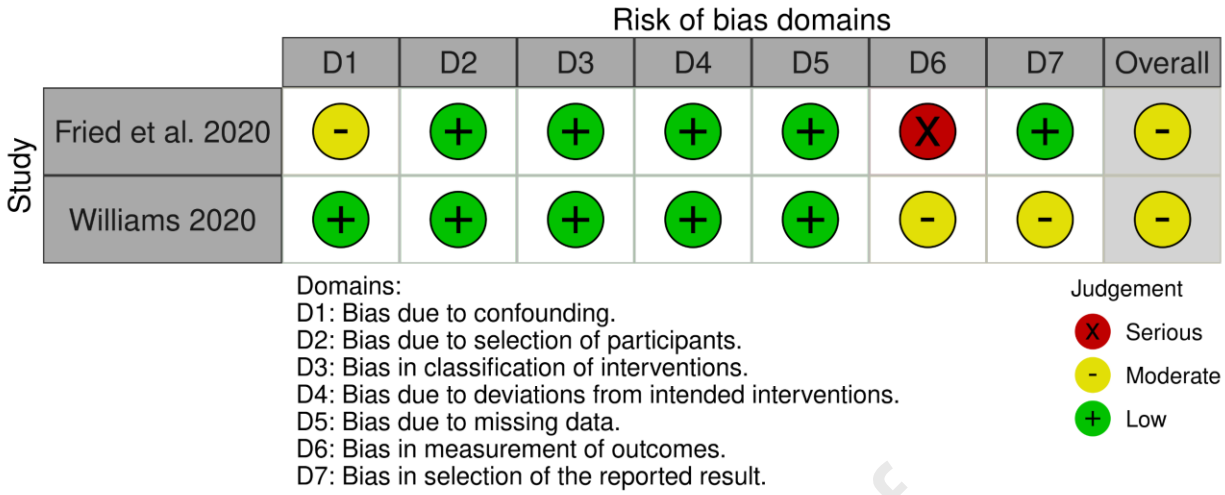
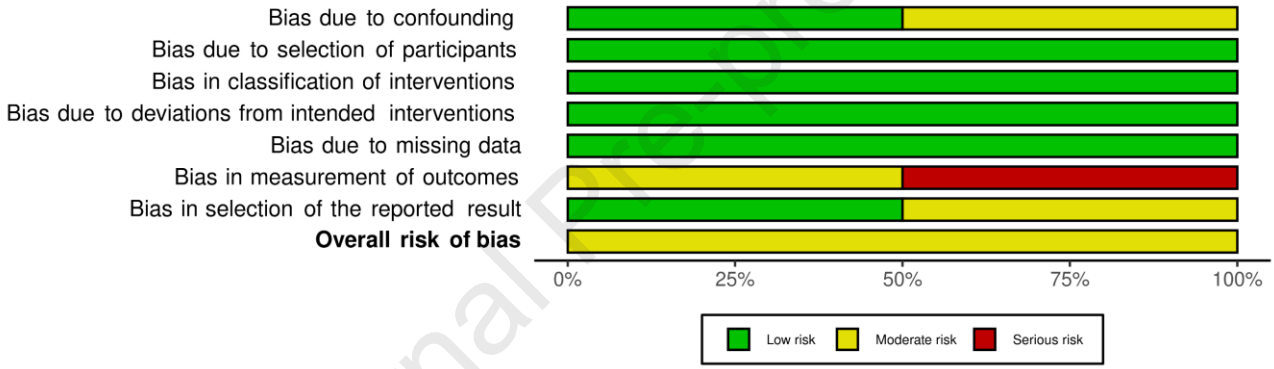






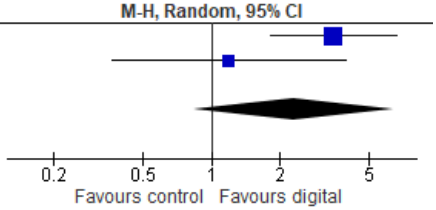




Study or Subgroup	Digital intervention Events	Total	Non-intervention/Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Fried et al. 2020	74	87	153	246	61.4%	3.46 [1.82, 6.58]
Williams et al. 2021	11	21	11	23	38.6%	1.20 [0.37, 3.92]
Total (95% CI)		**108**		**269**	**100.0%**	**2.30 [0.84, 6.33]**
Total events	85		164			

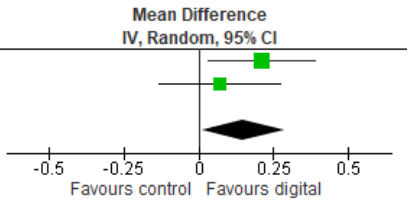
Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 2.38$, df = 1 (P = 0.12); $I^2 = 58\%$

Test for overall effect: Z = 1.61 (P = 0.11)



Study or Subgroup	Digital intervention Mean	SD	Total	Non-intervention/Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Weisman et al. 2018	0.93	0.18	19	0.72	0.36	20	56.6%	0.21 [0.03, 0.39]	2018
Williams 2020	0.88	0.4	43	0.81	0.55	43	43.4%	0.07 [-0.13, 0.27]	2020
Total (95% CI)			**62**			**63**	**100.0%**	**0.15 [0.01, 0.29]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 2.15 (P = 0.03)



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