

Testing the Efficacy of a Smartphone Application in Improving Medication Adherence, Among Children with ADHD

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ABSTRACT

Background: Adherence to medication is a key factor for successful treatment of children with ADHD. However, most children do not adhere to their pharmacotherapy regimen, and have no contact with their physician during the first month of pharmacotherapy. A mobile health (mHealth) approach may bridge the gap between physicians and patients, allowing for more frequent communications as well as better monitoring of adherence to the prescribed treatment.

Method: The study sample included 39 children with ADHD (27 boys), aged 9.56 ± 2.41 years. Participants were randomly assigned to one of the following two groups: (1) a study group in which participants and their parents were prompted to use a mobile application (i.e., mobile app or app); or to (2) a control group in which participants were treated as usual, without the app. Pill counts, which is a common strategy for confirming medication adherence, was recorded at week 4 and week 8. Clinical assessment conducted at baseline, week 4, and week 8.

Results: Participants who were prescribed with the app demonstrated higher overall pill counts over 8-weeks period, $F=4.33$, $p<.05$. In addition, a significant improvement in total CRS score was found among the study group compared to controls in week 4 and week 8, $F=4.74$, $p<.05$.

Conclusions: The current study provides initial support for the feasibility of a new mobile app in promoting adherence to stimulants among youth with ADHD.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most prevalent neurodevelopmental disorder, affecting approximately 6-10% of school-age children (1). Left untreated, ADHD can lead to impairments in multiple domains, including academic performance, productivity and social adjustment (2). Along with behavioral therapies, stimulants are among the first-line treatments for ADHD (3, 4). However, poor adherence can make even the best medication become ineffective. Adherence is defined as the extent to which a patient's actions correspond to the treatment recommendations of the healthcare provider with respect to timing, dosage and frequency of taking medication during the prescribed length of time (5). Adherence to treatment is usually lower for children as compared to adults, and for psychiatric patients as compared to non-psychiatric (medical) patients (6). As such, children with ADHD constitute a risk group for low medication adherence (7).

One of the main challenges for physicians treating children with ADHD is to maintain their patients' adherence to pharmacotherapy. A recent review of adherence and discontinuation rates for ADHD interventions showed that almost half (44%) of all individuals originally enrolled to these studies were withdrawn from it ahead of time (8). Discontinuation rates for stimulants are generally high, ranging between 19% for long-acting and 38% for short-acting stimulants in individuals of all ages (9). The discontinuation rates of children aged 6-12 years old are especially high (10). An analysis of the medical records of a large urban elementary school cohort from the Philadelphia area showed that only one in five of those prescribed with MPH adhered to treatment (7). Similar

adherence rates were found in another community-based study conducted in Germany (11).

Smartphone applications (mobile apps) are being increasingly recognized for their potential utility in promoting healthcare delivery and health-supportive behaviors and habits (12). Encouraging adherence to treatment, including pharmacotherapy, is one way by which mobile apps can promote healthcare at the individual level (13, 14). Having that said, however, no study we know of has tested the usefulness (i.e., utility) of a mobile app for managing adherence to stimulant medications among individuals with ADHD.

The aim of the current investigation was to assess the utility and effectiveness of a mobile app in improving adherence to stimulants among children with ADHD. We hypothesized that children whose parents are offered to engage with the app will demonstrate better adherence and improvement in clinical symptoms compared to children treated as usual.

METHOD

PARTICIPANTS AND RECRUITMENT

Thirty-nine children (27 boys, 12 girls) who met criteria for a diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (15) were enrolled in the study. Participants' mean age was 9.56 \pm 2.41 years (range 6-16 years). Participants were either drug naïve ($n = 18$; 46.2%) or already treated for ADHD with stimulant medications prior to their participation in the study ($n = 21$; 53.8%). The medications prescribed for participants as well as the number of individuals that completed each of the visits are detailed in Table 1.

Recruitment took place between December 2015 and August 2016 in a child and adolescence psychiatry outpatient unit in a large tertiary medical center in Israel. Parents signed an informed consent prior to child's participation in the study. Participants were randomly assigned to one of the following: the study group ($n = 19$) which was provided with the app, and the control group ($n = 20$) which was treated as usual, without the app. The groups were matched for age, sex distribution, socioeconomic status and type of ADHD medication. A research assistant guided and trained the study group parents in using the mobile app during their first visit to the clinic (baseline visit, T1). Both parent and child were debriefed immediately after completing the study. The research received the approval of the Institutional Review Board (IRB).

Three subjects ($n = 3$) who were originally randomized

Table 1. Sample Characteristics

Measure	Total Sample	App	Controls	Statistics
			(p-value)	
Male/Female	27/12	14/5	13/7	.56
Age, mean (SD)	9.56 (2.41)	10.21 (2.21)	8.93 (2.47)	.09
ADHD Medications, n				
Methylphenidate	21	10	11	
Mixed amphetamine salts	6	33		
Dexmethylphenidate	6	5	1	
Lisdexamfetamine	6	1	5	
Study Visits Completed, n (%)				
T1	5 (12.82%)	-	5 (26.31%)	
T2	10 (25.64%) 7 (35%)	3 (15.79%)		
T3	24 (61.54%)	12 (60%)	12 (63.16%)	

to the study group were excluded from the study during the screening phase as they failed to download the app as requested.

PROCEDURE AND DIAGNOSTIC INSTRUMENTS

Diagnostic interviews with children and parents were conducted by a qualified child and adolescent psychiatrist. An assessment of child's ADHD symptoms was conducted with the Attention Module of the Kiddie-SADS (16) and the MINI-KID (17) was used for screening of symptoms of comorbid psychiatric disorders.

Pill counts were recorded by the parent in a paper medication log that was not part of the application. The log was completed daily by the parents and reviewed by the clinician while children and their parents were visiting the clinic or during a phone interview at 4-week and 8-week post-study initiation (T2 and T3, respectively). The Clinician Rating Scale (CRS; 18), the ADHD-Rating Scale (ADHD-RS; 19), and the Clinical Global Impression (CGI; 20) were administered at T1, T2 and T3 to assess improvement in levels of ADHD symptom severity. CGI-Improvement subscale was administered only at T2 and T3 as it meant to capture change from baseline assessment.

THE ICON™ MOBILE APP

The app was developed by a local (Israeli) software company that specializes in digital health. The app development, as well as the current efficacy study, was sponsored by Janssen Israel, pharmaceutical companies of Johnson & Johnson. The app was designed with the purpose of allowing patients or their parents to report their clinical status following initiation of prescription or after changing medication dosage. The overarching purpose of the app

was to facilitate the communication between the patient and the treating physician.

Furthermore, the app included questions regarding the severity of child's ADHD symptoms and potential side effects. Parents were asked to answer these questions once a week via their smartphone device. The survey included 11 questions and referred to the following domains: (1) Decline in appetite (yes/no); (2) Child's mood (rate 1–5 on a Likert-scale, with 5 reflecting more positive affect); (3) Child's functioning in social circumstances (rate 1–5); (4) Child's dealing with learning/school setting (rate 1–5); (5) Child's function at home (rate 1–5); (6) Parental satisfaction with the medication (rate 1–5); (7) Child's severity of hyperactivity (rate 1–5); (8) Impulsivity (rate 1–5); and (9) Attention (rate 1–5) symptoms; (10) Child's level of organization (rate 1–5); (11) Child's experiences of stomach aches or headaches (yes/no). The app is designed to afford the treating physician ability to review the questionnaires completed by the parents at any given time. In our study the treating child psychiatrist reviewed the weekly surveyed questions completed by the parents at visit 2 and visit 3.

The app may also function as a medication reminder. By default, the app was set to remind to take the medication at 7am every morning. Users have the option to set the trigger notification to the time that suits them the most. Importantly, both the mobile app and the web-portal associated with it include a host of information for parents and children regarding ADHD disorder and the different ways of treatment that exist (thus, promoting psycho-education). Materials included short clips, articles and links to additional reading materials.

Noteworthy, although the app was curated by Janssen, it is open for use by all physicians and patients regardless of the brand/type of medication prescribed. The app can be downloaded from the Google Play (<https://play.google.com/store/apps/details?id=com.ideomobile.icon>) and the iTunes (<https://itunes.apple.com/il/app/icon4adhd/id726377799?mt=8>) app stores. The official website of the app can be reached here (<https://icon4adhd.co.il/login.html>).

STATISTICAL ANALYSES

The analysis was conducted using IBM statistical package for social sciences (SPSS) version 20.0. Repeated-measures analysis of variance (ANOVA) was computed to examine the effect of the app on pill counts and symptoms severity for each of the study visits (visits/time was treated as the within-subject variable and group identity treated as the between-subject variable). Pill-counts, CRS score,

ADHD-RS score and CGI-Severity score were handled as dependent variables, each analyzed separately. The rates of improvers/deteriorators (i.e., CGI-I score) were assessed with Chi-square or Fisher's Exact Test (when n was < 5). Huynh-Feldt test was employed when sphericity was not assumed. In such cases, post-hoc comparisons were calculated with Mann-Whitney test. Finally, missing values were completed using the Last Observation Carried Forward (LOCF) approach.

RESULTS

The distribution of ADHD sub-types among the 39 subjects were: combined presentation ($n = 18$, 46.2%), inattentive presentation ($n = 16$, 41.0%), hyperactive/impulsive presentation ($n = 4$, 10.3%), and ADHD-NOS ($n = 1$, 2.6%), with no significant difference between the groups, $p > .05$. Children were diagnosed with several psychiatric comorbidities, including: learning disorders ($n = 8$, 20.51%), oppositional-defiant disorder ($n = 11$, 28.21%), and anxiety disorders ($n = 4$, 10.26%). The latter included specific phobia ($n = 2$), social anxiety disorder ($n = 1$) and generalized anxiety disorder ($n = 1$).

A group main effect was found for pill-counts, $F_{(1,32)} = 4.331$, $p < .05$, $\eta^2 = .12$. Specifically, participants who were prompted to use the app demonstrated higher overall adherence to medication compared to those in the control group (see Figure 1). Post-hoc comparisons with Mann-Whitney U showed that individuals who used the app consumed significantly more pills than controls at week 8 ($Mdn = 20.74$ vs. 13.40), $U = 81.00$, $p < .05$, but not at week 4 ($Mdn = 19.29$ vs. 15.23), $U = 108.50$, $p > .05$ (see Table 2).

Group main effect in CRS score was found, $F_{(1,30)} = 4.74$, $p < .05$, $\eta^2 = .13$, as the study group participants demonstrated higher scoring, above and beyond study visit. Time by group interaction was significant, Huynh-Feldt $F_{(2,64)} = 4.57$, $p < .05$, $\eta^2 = 0.1$, showing a linear trend across time, $p < .05$. Post-hoc comparisons with Mann-Whitney U indicated that the CRS scores did not differ between groups during baseline assessment (T1; $Mdn = 21.13$ vs. 18.93, respectively), $U = 168.50$, $p > .05$, but that the study group participants showed better scoring compared to controls at week 4 (T2): $Mdn = 20.92$ vs. 13.17), $U = 77.50$, $p < .05$, and week 8 (T3); $Mdn = 21.34$ vs. 12.63, respectively), $U = 69.50$, $p < .01$ (see Table 2 & Figure 2). No significant differences in ADHD-RS or CGI scores were found.

Finally, analysis found no difference in the levels of

Figure 1. Comparing pill counts (level of medication adherence) between the study group (app users) and the control group

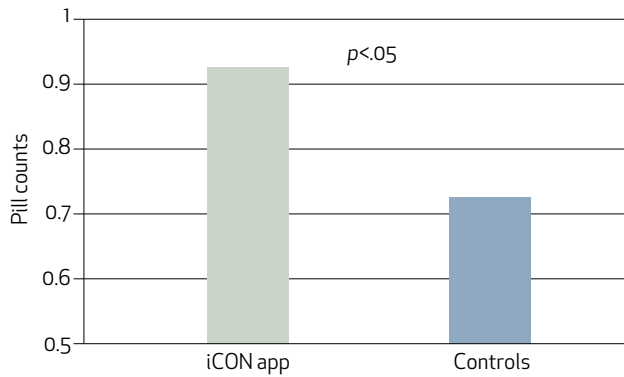
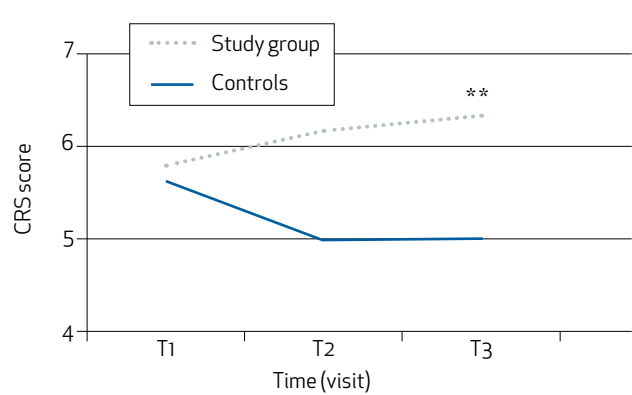


Figure 2. Comparing CRS scores between the study group and the control group at baseline (T1), week 4 (T2), and week 8 (T3)



* $p < .05$; ** $p < .01$

Table 2. Comparison of Clinical Measurements at Baseline (T1), 4 Weeks (T2), and 8 Weeks (T3) Between the Study Group (mobile app users) and Control Group

Measure	N App / Controls	App	Controls	Statistics (p-value)
Pill Counts				.04
T2	19/15	0.92 ± 0.18	0.74 ± 0.37	.20
T3	19/15	0.93 ± 0.18	0.72 ± 0.36	.015
CRS Total				.04
T1	19/20	5.79 ± 1.43	5.60 ± 1.39	.53
T2	19/15	6.16 ± 1.12	5.00 ± 1.60	.02
T3	19/15	6.32 ± 0.95	5.00 ± 1.60	.008
ADHD-RS				.28
T1	19/20	25.22 ± 9.57	31.60 ± 9.86	.17
T2	18/15	18.16 ± 7.77	17.46 ± 10.28	.62
T3	19/15	13.83 ± 7.86	16.66 ± 9.77	.58
CGI-S				.61
T1	19/20	5.11 ± 0.74	4.90 ± 0.79	.40
T2	19/15	3.84 ± 1.06	3.80 ± 1.37	.75
T3	19/15	3.05 ± 1.43	3.66 ± 1.04	.21
CGI-I, n (% improvers)				
T2	18/15	12 (66.6)	8 (53.3)	.43
T3	18/15	12 (66.6)	10 (66.6)	1.0

Note. CRS = Clinician Rating Scale; ADHD-RS = ADHD Rating Scale; CGI-S = Clinical Global Impression Scale–Severity; CGI-I = Clinical Global Impression Scale–Improvement

medication adherence and clinical parameters between medicated and drug-naïve participants.

DISCUSSION

Adherence to medication is a key factor for successful treatment of children with ADHD (21). Literature suggests that the majority of children with ADHD are

treated by primary care providers (22). Unfortunately, the quality of ADHD care in this setting, such as frequency of follow-up meetings, is often poor (23). For example, it was claimed that most children with ADHD have no contact with their physician during the first month of medication treatment (24). A mobile health (mHealth) approach seems viable in this respect, as it has the potential to bridge the gap between physicians and patients, allowing for more frequent communications as well as better monitoring of adherence to the prescribed treatment.

Indeed, our findings support the utility of mobile app intervention for promoting adherence in psychiatric populations, and more so among children with ADHD. The current findings show that the iCON™ app is a workable model for improving implementation of pharmacotherapy in this population. Specifically, children of parents who were prompted to download and use the app received daily notifications to remind their children to take medication, completed questionnaires concerning the severity of symptoms and potential side effects on a weekly basis, and were exposed to educational materials about ADHD, were more likely to follow their prescription as instructed. Notably, this effect, as evidenced by the parameter of pill counts, was stronger after eight weeks of using the app than it was after four weeks.

Of note is that children in the app group showed improved adherence to treatment, measured by the CRS and pill counts. However, the mobile app had no significant effect on severity of ADHD symptoms, measured by the ADHD-RS and CGI.

We do not have an explanation for the lack of effect of the app on severity of ADHD symptoms. It could be that a larger sample size or a longer-term follow-up are needed to expose an effect if such exists. Following participants for a longer time will allow more ecological understanding of adherence patterns in these populations. In addition, users' level of interaction with the app (e.g., total usage time, usage frequency) was not documented or logged by the app and so it could not be analyzed together with clinical parameters. For instance, although the app offers a host of online educational materials concerning ADHD symptoms and intervention practices it does not save users' level of engagement with these materials.

Several factors were shown to associate with poor adherence among individuals with ADHD, including male gender, lower intelligence, lower socioeconomic status, multiple daily regimen and the presence of fewer ADHD symptoms (e.g., 25-27). Conversely, individuals with high levels of adherence to stimulants usually have more severe ADHD symptoms and are shown to be more educated about the disorder (28, 29). Whereas some of these factors are less relevant for the current study given the homogeneous nature of our cohort, they should be considered by researchers aiming to test the effectiveness of mobile interventions in the future. Obviously, accounting for more variables also necessitates larger sample size, similar to what has been done with non-psychiatric populations (30, 31).

Limitations of the study include the relatively small sample size and the fact that only 61.5% of the children and parents initially enrolled to the study completed all three visits. The relatively high drop-out rate goes in line with our clinical impression that many parents of children with ADHD tend not to adhere to regular follow-up scheduled visits. The fact that many parents of children with ADHD fail to show up for scheduled visits supports the need to develop other means for remote monitoring and management of children with ADHD such as the mHealth solution mobile app (32). It is noteworthy that the app itself was relatively easy to use and required only authentication of users' email to initiate its use. The app's functionality did not constitute a barrier for participation of parents in the study.

In conclusion, the current study is a first step towards validating the feasibility of a mHealth approach in promoting medication adherence among children with ADHD.

References

- Biederman J. Age-dependent decline of symptoms of attention deficit hyperactivity disorder: Impact of remission definition and symptom type. *Am J Psychiatry* 2000;157:816-818.
- Wright N, Moldavsky M, Schneider J, et al. Practitioner review: Pathways to care for ADHD - a systematic review of barriers and facilitators. *J Child Psychol Psychiatry* 2015;56:598-617.
- The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Vol. 56, *Archives of General Psychiatry*, 1999; pp. 1073-1086.
- Storebø OJ, Ramstad E, Krogh HB, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). In: Storebø OJ, editor. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley, 2015; p. CD009885.
- Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* [Internet]. 2005 Aug 4 [cited 2016 Nov 29];353:487-497.
- Hack S, Chow B. Pediatric psychotropic medication compliance: A literature review and research-based suggestions for improving treatment compliance. *J Child Adolesc Psychopharmacol* 2001;11:59-67.
- Marcus SC, Durkin M. Stimulant adherence and academic performance in urban youth with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2011;50:480-489.
- Frank E, Ozon C, Nair V, Othee K. Examining why patients with attention-deficit/hyperactivity disorder lack adherence to medication over the long-term. *J Clin Psychiatry* 2015;76:e1459-1468.
- Lachaine J, Beauchemin C, Sasane R, Hodgkins PS. Treatment patterns, adherence, and persistence in ADHD: A Canadian perspective. *Postgrad Med* 2012;124:139-148.
- Chen C-Y, Yeh H-H, Chen K-H, 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;21:265-273.
- Garbe E, Mikolajczyk RT, Banaschewski T, et al. Drug treatment patterns of attention-deficit/hyperactivity disorder in children and adolescents in Germany: Results from a large population-based cohort study. *J Child Adolesc Psychopharmacol* 2012;22:452-458.
- Free C, Phillips G, Watson L, et al. The effectiveness of mobile-health technologies to improve health care service delivery processes: A systematic review and meta-analysis. *Cornford T, editor. PLoS Med* 2013;10:e1001363.
- Dayer L, Heldenbrand S, Anderson P, Gubbins PO, Martin BC. Smartphone medication adherence apps: Potential benefits to patients and providers. *J Am Pharm Assoc* 2013;53:172.
- Hamine S, Gerth-Guyette E, Faulx D, Green BB, Ginsburg AS. Impact of mHealth chronic disease management on treatment adherence and patient outcomes: A systematic review. *J Med Internet Res* 2015;17:e52. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25803266>
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. Am Psychiatr Assoc 2013;991.
- Kaufman J, Birmaher B, Brent D, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;36:980-988.
- Sheehan DV, Sheehan KH, Shytle RD, et al. Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID). *J Clin Psychiatry* 2010;71:313-326.
- Kemp R, Kirov G, Everitt B, Hayward P, David A. Randomised controlled trial of compliance therapy. 18-month follow-up. *Br J Psychiatry* 1998;172:413-419.
- Dupaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale-IV: Checklists, norms, and clinical interpretation. *J Psychoeduc Assess* 2006;24:172-178.
- Guy W. ECDEU assessment manual for psychopharmacology. Rev. Rockville, Md.: U.S. Dept. of Health Education and Welfare Public Health Service Alcohol Drug Abuse and Mental Health Administration National Institute of Mental Health Psychopharmacology Research Branch, 1976.
- Atzori P, Usala T, Carucci S, Danjou F, Zuddas A. Predictive factors for persistent use and compliance of immediate-release methylphenidate:

- A 36-month naturalistic study. *J Child Adolesc Psychopharmacol* 2009;19:673-681.
22. Zito JM, Safer DJ, dosReis S, et al. Psychotherapeutic medication patterns for youths with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med* 1999;153:1257-1263.
 23. Zima BT, Bussing R, Tang L, et al. Quality of care for childhood attention-deficit/hyperactivity disorder in a managed care medicaid program. *J Am Acad Child Adolesc Psychiatry* 2010;49:1225-1237.
 24. Epstein JN, Kelleher KJ, Baum R, et al. Variability in ADHD care in community-based pediatrics. *Pediatrics* 2014;134:1136-1143.
 25. Ibrahim ESR. Rates of adherence to pharmacological treatment among children and adolescents with attention deficit hyperactivity disorder. *Hum Psychopharmacol Clin Exp* 2002;17:225-231.
 26. Gau SSF, Shen H-Y, Chou M-C, et al. Determinants of adherence to methylphenidate and the impact of poor adherence on maternal and family measures. *J Child Adolesc Psychopharmacol* 2006;16:286-297.
 27. Faraone S V, Biederman J, Zimmerman B. An analysis of patient adherence to treatment during a 1-year, open-label study of OROS(R) methylphenidate in children with ADHD. *J Atten Disord* 2007;11:157-166.
 28. Park J, Kim B. Comorbidity and factors affecting treatment non-persistence in ADHD. *J Atten Disord* 2015; Available from: <http://jad.sagepub.com/cgi/doi/10.1177/1087054715587097>
 29. Gajria K, Lu M, Sikirica V, et al. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder - a systematic literature review. *Neuropsychiatr Dis Treat* 2014;10:1543-1569.
 30. Liu X, Lewis JJ, Zhang H, et al. Effectiveness of electronic reminders to improve medication adherence in tuberculosis patients: A cluster-randomised trial. Metcalfe JZ, editor. *PLOS Med*. 2015;12:e1001876.
 31. Choudhry NK, Krumme AA, Ercole PM, et al. Effect of reminder devices on medication adherence. *JAMA Intern Med* 2017;314:1818-1831.
 32. Simons L, Valentine AZ, Falconer CJ, et al. Developing mHealth remote monitoring technology for attention deficit hyperactivity disorder: A qualitative study eliciting user priorities and needs. *JMIR mHealth uHealth* 2016;4:e31. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/27009498>