Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 26 July 2018 doi:10.20944/preprints201807.0504.v1

Peer-reviewed version available at *J* **2018**, *1*, 8; doi:10.3390/j1010008

Review

Gamification Concepts to Promote and Maintain Therapy Adherence in Children with Growth Hormone Deficiency

Short Title: Gamification Concepts in Children with Growth Hormone Deficiency

Sally Radovick [1], Eli Hershkovitz [2], Aline Kalisvaart [3], Marco Koning [4], Kristine Paridaens [5] and Maged N. Kamel Boulos [6,*]

[1] Department of Pediatrics, Rutgers-Robert Wood Johnson Medical School, USA
[2] Pediatric Endocrinology Unit, Soroka Medical Center & Faculty of Health Sciences, Ben-Gurion University, Beer Sheva, Israel
[3] Kind-visie, Utrecht, Netherlands
[4] StoryConnect, Wageningen, Netherlands
[5] Ferring Pharmaceuticals, Saint Prex, Switzerland
[6] Moray College, University of the Highlands and Islands, Elgin, United Kingdom
* Correspondence: mnkboulos@ieee.org; Tel.: +xx-xxx-xxx-xxxx

Abstract: Growth hormone (GH) deficiency affects up to 1 in 4,000 children and is usually treated with daily injections of GH whilst the child is still growing. With children typically diagnosed around 5 years old, this can mean over 10 years of therapy, which can place a considerable burden on the child and parent. Over three-quarters of children are estimated to be not fully compliant with therapy, which can compromise their chances of attaining their target height. In recent years, interactive mobile health (smart phone or tablet) interventions using game-like concepts, so called 'gamification', have increased in popularity and have demonstrated success in promoting positive self-management behaviour in children with chronic conditions, such as diabetes. The application of gamified interventions has the potential to support adherence to therapy and positive behaviour in children with GH deficiency in a number of ways: 1) By providing education in a format that the child understands and accepts (e.g. using behavioural constructs to facilitate explaining why adherence is important); 2) By providing a mechanism to reduce the anxiety and stress associated with administering the injection (e.g. diversion with a virtual pet); and 3) By providing feedback to encourage on-going engagement (e.g. rewards, progression through levels).

Keywords: app; somatotropin; serious games; gamification; digital; mobile health

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List of Abbreviations:

BMI – body mass index
CI – confidence interval
CMHD – common mental health disorders
DMN – default mode network
fMRI – functional magnetic resonance imaging
GH – growth hormone
mHealth – mobile health
sMRI – structural magnetic resonance imaging
VR – virtual reality

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Peer-reviewed version available at J 2018, 1, 8; doi:10.3390/j1010008

1. Introduction

Growth hormone (GH; also known as somatotropin) deficiency affects approximately 1 in 4,000 to 1 in 10,000 children and typically becomes evident at around 5 years old [1,2]. A child diagnosed at this age may require daily injections of GH for over 10 years, which can place a considerable burden on both the child and parent and may result in suboptimal treatment compliance [3]. It has been estimated that up to 82% of paediatric patients are not fully compliant, with missing more than one GH dose per week shown to significantly compromise linear growth ($p<0.01$), reducing the chances of attaining normal or near-normal adult height [3,4,5]. Patients who are receiving GH therapy are typically monitored around 2-4 times per year for growth progress and to adjust GH dosage [6]. In order for patients to receive the full benefit of GH therapy, there is a need for convenient and feasible innovations to facilitate monitoring and maintenance of compliance and adherence.

Play can be a useful tool for helping children to process their diagnosis, illness, and treatment [7]. Such exercises and games have been shown to help reduce children's distress and anxiety in preparation for medical procedures [8]. As children increasingly turn to mobile gaming for entertainment (a reported 86% of 6-10 year olds regularly play video games) [9], researchers are investigating whether it is possible to harness this medium to engage with patients [10]. In recent years, interactive mobile health (mHealth) interventions have emerged as a strategy to tackle the challenges young patients face in coping with chronic conditions [11]. mHealth interventions are mobile-based (smartphone or tablet) applications designed to educate, train and provide treatment support for patients outside of the clinic. The term 'gamification' refers to the application of game-like concepts or elements, (e.g. quests and goals, achievements and badges, leader boards [competition], points, levels, virtual goods and rewards, in-game friends and teams [collaboration and social scaffolding], etc.) in non-game contexts [12,13]. There is growing evidence to suggest that the application of 'gamification' concepts can influence and promote positive, lasting behavioural change in various health conditions and age groups (including children) through the design of digital games which carefully target patient needs [12,14,15]. The aim of this paper is to explore how gamification concepts and mHealth strategies could be combined to address the challenge of adherence in children receiving GH therapy to support and improve outcomes.

2. Overview of gamification strategies for health

Gamification in health offers a creative and innovative approach to tackling adherence in children with chronic conditions such as GH deficiency. Serious games are increasingly offered as mobile apps that can be used to entertain players while educating and training them ('edutainment') to promote positive behaviour [12,16]. The application of game mechanics (play actions and the associated parameters and rules) in health can help to turn serious routine responsibilities e.g. administration of daily injections, into a fun, engaging activity by leveraging gaming dynamics (gameplay sequences, behaviours and complexity, the products of game mechanics), behavioural constructs, and incentives to support self-management [17,18]. There are a number of integral pathways of influence and feedback which need to be considered to ensure the development of successful gamification strategies for positive behavioural change, including the impact of game elements, mechanics and dynamics on both neuro-chemical and psychological pathways (Figure 1).

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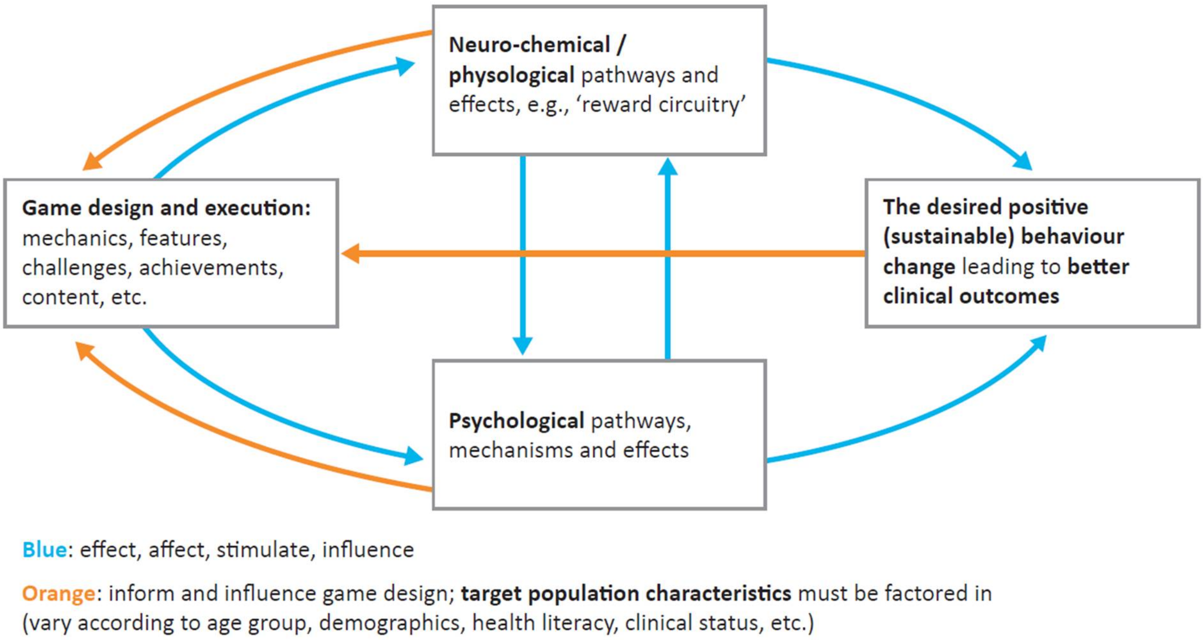

Figure 1. Integral pathways of influence and feedback for the development of successful gamification strategies for behavioural change.

Game mechanics and the resulting game dynamics aim to provide the user with challenges, rewards, fun engagement and socialisation through use of game elements, such as points, leader boards, badges, levels and coaches in the form of avatars (e.g. virtual-self or pet) [12,[19]]. The persuasive architecture of gamification relies on the combination of ingredients that make a task fun and engaging [[19]]. It has been proposed that there are 7 core ingredients for gamification that can be utilised to inspire behavioural change: Goal setting, challenges, feedback, reinforcement, monitoring/comparing progress, social connectivity, and fun/playfulness [[19]].

There is growing scientific evidence to suggest that gamification strategies can directly influence neurochemical networks in the brain through activation of 'reward circuitry' and dopaminergic pathways [[20],[21],[22]]. Studies show that incentives and rewards can promote educational learning and positive behavioural change through direct activation of neural mechanisms of reinforcement [[21],[22]]. Using methods including structural Magnetic Resonance Imaging (sMRI) and functional Magnetic Resonance Imaging (fMRI), rewards have been shown to produce direct changes in the brain resulting in enhanced performance in demanding cognitive tasks such as working memory [[22]]. Education in a game-based environment has also been associated with deactivation of Default Mode Network (DMN) regions, thus promoting a deeper level of learning [[23]].

In addition to the direct neurological effects of gamification, consideration must be given to psychological pathways. Motivation is one of the most crucial psychological drivers of all human behaviour [[24]]. There are two types of motivation which are critical for sustained behavioural change: intrinsic motivation (the internal desire to do an activity e.g. out of enjoyment) and extrinsic motivation (dependent on a reward received whenever an activity is completed) [[24]]. The use of extrinsic motivation in mHealth interventions can serve to establish a new behaviour, but when used alone can become meaningless over time resulting in a loss of motivation [[25]]. The Octalysis framework organises motivating factors into 8 core drives of gamification: Meaning, Empowerment, Social influence, Unpredictability, Avoidance, Scarcity, Ownership and Accomplishment [[26]]. It is proposed that games must appeal to one or more of these motivational drivers in order to keep users engaged with an app over time [[26]]. In order to ensure sustainable behavioural change without relapse, gamification must go beyond simple achievements and points. Patients must be able to self-

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identify with goals that are meaningful to them, as this will help the patient to accept the intrinsic value of the task resulting in more autonomous, internalised behaviours [25].

In order to successfully effect the desired long-lasting health and behaviour changing outcomes, all the involved human, personal and psychological factors of the target population must be considered (e.g. age group, demographics, health literacy, clinical status), as this will not only affect how users will engage with the game, but also how they are persuaded via the game elements to positively change their behaviour without relapse. Another important ingredient is 'iterative development', which involves working with key stakeholders (i.e. children, parents and healthcare professionals), including a good representative sample of end users (i.e. children with chronic illnesses), to test and refine features of the game repeatedly early in the process to help avoid late-stage failure [27]. Improved understanding of the feedback between the integral pathways of influence helps to inform the development of games to ensure an effective and relevant experience for the end user.

3. How could gamification contribute to improved adherence to GH therapy?

Non-adherence to GH therapy can arise from a multitude of inter-related psychological, socio economic and technical issues [3]. Children and parents' beliefs about GH therapy as well as their relationship with healthcare professionals are critical for the maintenance of adherence [28]. Negative beliefs about medicines have been associated with more negative illness perceptions in patients with long term conditions which can affect patient quality of life and self-management behaviour, including adherence to medication [29]. Unlike other chronic conditions, such as diabetes, non-adherence to GH therapy may not have immediate acute consequences and therefore may go unnoticed for longer. It is therefore crucial that both parents and children are made aware of the potential consequences associated with missed doses when initiating GH therapy, both clinical (e.g. reduced height velocity) and economic (e.g. wasted medicine) [3]. Changing patients' attitudes regarding the implications of missed doses (via effective in-game education) is the first step toward positively changing their behaviour without relapse, resulting in perfect compliance and continued adherence.

Expectations and beliefs about GH therapy need to be agreed upfront to ensure that patients set realistic goals. Education through mobile games could help to reinforce patient understanding about GH deficiency and coach patients about the benefits of continuing with therapy, especially in young children who often rely on play-based learning to make sense of the world around them. Patients can also feel a sense of disappointment due to unrealistic expectations and goals [28]. A smartphone app could help patients to track their growth, charting their progress toward realistic goals set by physicians. As injections must be delivered daily, it can also be difficult for parents to find an appropriate time to schedule injections that fits into both the parent and child's routine [3]. Use of a mobile app may help to establish daily injections as part of the child's bedtime routine and provide prompts when doses are missed.

Serious games can help patients to establish important self-management behaviours in a fun and positive environment. Monster Manor (Ayogo; The Sanofi Group) is a smartphone app developed for children aged 5-10 years with type 1 diabetes [30]. The game aims to encourage children to take more responsibility for their diabetes management by rewarding their efforts in logging and tracking blood sugar measurements. Virtual coins earned in the game can be used to build monsters and furnish the rooms within the manor house [30]. At the end of an evaluation undertaken 15 months after launch, the Monster Manor app had been downloaded 1,238 times (Apple: 857, Android: 381) [31]. After 1 year there were 50-75 active users per month (compared with a peak of 445 shortly after launch). In total, 7,699 capillary blood glucose readings were logged. Of the 21 players completing the follow-up questionnaire, 40% played the game for longer than 1 month and 19% reported a positive impact on the frequency of blood glucose testing [31]. Monster Manor has since been adapted to work wirelessly with an activity monitor to encourage children to increase their daily step count

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and active minutes [[32]]. This version of the game was evaluated in a randomized, 4-week crossover study of 42 healthy students in a school based environment (11.3 ± 1.2 years old and 0.28 ± 1.29 body-mass index [BMI] z-score) [32]. When children were exposed to the game, an increase compared with the control phase of 2,934 steps per day (p=0.0004, 95% confidence interval [CI] 1,434-4,434) and 46 active minutes per day (p=0.001, 95% CI 20-72) from baseline (12,299 steps/day and 190 active minutes/day) was observed [[32]]. The success of these games highlights the potential for gamification to promote positive self-management behaviour in children with GH deficiency.

Anxiety over administration can pose a considerable barrier to self-management in children with GH deficiency due to the discomfort associated with daily subcutaneous injections [3]. In an Internet survey of 69 parents who had children with GH deficiency, 37% of the parents indicated that their children felt anxious about administration of GH [[33]]. Coping behaviours, such as relaxation (e.g. breathing exercises, imagery, progressive muscle relaxation) or distraction techniques (e.g. counting backward, imagery, repeating a mantra, solving problems), can be beneficial for the relief of anxiety associated with painful medical procedures in children [[34]]. The application of gamification concepts for the management of anxiety and distress has recently been investigated in patients with chronic common mental health disorders (CMHDs) [[35]]. Flowy (PlayLab London) is a smartphone app which delivers breathing retraining exercises for anxiety, panic and hyperventilation symptom management [[36]]. Patients control elements within the game by blowing into the microphone on their mobile device. An unblinded, Web-based, parallel-group, randomized, controlled, pilot trial was conducted in 63 participants to assess the impact of the game on health outcomes [[35]]. All respondents found Flowy to be a useful intervention and 89% said they would recommend it to friends. Use of Flowy resulted in a significant decrease in panic and hyperventilation and an increase in quality of life scores in intervention participants from baseline to Week 4 (Table 1) [35]. Similarly, it may be possible to implement gamified breathing exercises in children with GH deficiency to distract them from any feelings of anxiety or discomfort associated with daily injections. Another potential option is to use virtual reality (VR) to distract children from the moment of injection. VR platforms have recently been shown to provide a significant amount of relief in patients with chronic pain [[37]]. This intervention works by saturating sensory pathways with an immersive experience, and can be conveniently delivered using ordinary smartphones coupled with a low-cost VR headset.

Table 1. Psychometric questionnaire scores in response to an app ('Flowy') aimed at reducing anxiety, panic and hyperventilation in patients with chronic common mental health disorders [35].

	Intervention*			
Outcome	**Baseline**	**Week 2**	**Week 4**	**p†**
Panic (PDSS-SR)				
Mean (SD)	16.90 (5.24)	15.42 (5.42)	15.35 (5.78)	0.011
n	31	32	31	
Hyperventilation (Nijmegen)				
Mean (SD)	24.45 (9.79)	22.45 (10.61)	21.74 (11.27)	0.016
n	31	32	31	
Quality of life (Q-LES-Q-SF)				
Mean (SD)	32.11 (7.32)	35.67 (5.08)	35.89 (7.71)	0.005
n	31	19	18	

*Participants in the intervention group received free access to Flowy, whilst controls had no access to the app. PDSS-SR, Panic Disorder Severity Scale-Self Report; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form; SD, standard deviation. †Repeated-measures analysis of variance (ANOVA).

Practicalities and technical issues surrounding delivery of GH due to a lack of adequate training can also result in non-compliance [3]. Issues with drug delivery, such as preparation of the GH

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solution, device function, poor technique and incomplete transjection may affect the parent and child's perception of treatment [3]. Parents can feel shame if they are struggling to give treatment and may not want to admit this to their physician. Information on the duration of administration, quality of injection and side effects could be recorded within an app to identify and flag any potential issues. It is important to reassure parents that they are not alone and that it is not unusual to ask for assistance if treatment is not going to plan. mHealth interventions via smartphones and tablets could provide a convenient platform to provide support and advice on common problems at home.

Empowerment of patients plays a significant role in treatment adherence. It is important that children are given responsibility for their health. Virtual pets have been successfully utilised in a number of serious games to empower children to take responsibility for their lifestyle choices [38,39,40]. In these games, the child is given responsibility for the care of the virtual pet which develops in response to achievement of daily health goals, e.g. physical activity or fruit and vegetable intake. Virtual pets develop and grow over time in response to a player's actions and achievements, but can also suffer from 'poor care' if the player's achievements are lacking. Like real pets, they require the player to take care of them on a regular basis, resulting in a prolonged and continued interest in, and use of, these types of games (the Tamagotchi effect). A preliminary study has been carried out in 59 children evaluating virtual pets as a vehicle for promoting physical activity [40]. Children interacted with a mobile kiosk with a television displaying a virtual dog using a motion and voice detection device (Kinect for Windows). As part of the program, children were encouraged to set physical activity goals that were tracked by a wearable activity monitor. The virtual pet became more fit and learned more sophisticated tricks in response to achievement of activity goals. Those who interacted with a virtual dog for 3 days engaged in an average of 1.09 more hours of exercise daily than children who interacted with a similar computer system without a virtual pet ($p=0.001$) (Table 2). Results indicated that increased self-efficacy (one's belief in one's ability to accomplish a task) as a result of interacting with the virtual pet leads to increased favourable beliefs about physical activity. Children that interacted with the virtual pet also expressed marginally higher intentions to continue physical activity in the future when compared with the control group ($p=0.10$), suggesting sustained behavioural change [40]. A similar approach could be adopted in the context of GH therapy to establish more positive perceptions about treatment and self-management.

Table 2. Impact of interaction with a virtual pet on physical activity through mediation of self-efficacy and positive beliefs concerning the benefits associated with physical activity [40].

	Control Mean (SD)	Treatment Mean (SD)
Physical Activity Hours (3 day total)	5.86 (2.95)	9.14 (2.63)
Self-Efficacy*	3.58 (0.81)	4.01 (0.56)
Beliefs†	3.95 (0.72)	4.36 (0.62)
Future Intentions‡	3.85 (1.03)	4.25 (0.84)

SD, standard deviation; *Three interval scale items (1 = Not confident at all; 5 = Extremely confident) assessed the level of confidence that the children had about physical activity despite barriers including, asking parents to sign up for a physical activity; fatigue; and outside weather; †Four Likert scale items (1 = Don't agree at all; 5 = Completely agree) assessed the extent to which children agreed with statements about the consequence of being physically active: it would be fun; it would help me be healthy; it would give me energy; and it would help me spend more time with my friends; ‡A single interval scale item (1 = I am sure I will not be physically active; 5 = I am sure I will be physical active) assessed the extent to which children intended to engage in physical activity following completion of the study.

4. Limitations of mHealth and gamification

Gamified e-health is still a relatively nascent field and despite a growing body of evidence – a recent systematic review identified 46 such studies – there are relatively limited empirical data

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Peer-reviewed version available at *J* **2018**, *1*, 8; doi:10.3390/j1010008

available [12]. Most studies have focussed on short-term engagement through intrinsic reward [12], with data on how this translates to sustained behavioural change often lacking. Chronic disease management, however, is one of the most frequently studied areas (along with physical activity), and where tangible benefits have been seen [12,31,32,35]. Strong targeting to the user group, appropriate fresh content updates, a degree of customisation, and incorporation of emerging technologies and developments, will help to ensure the longevity of the mHealth tool will be greatly increased.

5. Conclusions

Gamification strategies and mHealth interventions may provide an innovative new tool to support patients and parents in coping with chronic illnesses beyond the clinic. mHealth interventions which rely on game mechanics have demonstrated success in promoting healthy self-management behaviour in children with chronic conditions, such as diabetes. Based on these encouraging results, we propose that application of gamification strategies could prove to be useful in tackling some of the root causes of non-adherence in children treated with GH therapy and should be a focus of investigation and development (Table 3).

Table 3. Summary of how mHealth and gamification can support adherence to GH therapy.

Educate Providing a source of information and guidance that is understandable and resonates with the child: • Why therapy is necessary — empowerment and taking responsibility of their own care • Setting realistic goals — motivate/positive belief • Importance of adherence — encourage on-going engagement e.g. through rewards, progression through levels, emotional bond with virtual pet etc. • Scheduling injections — reminders and establishing a routine
Reduce anxiety and stress over administration Providing mechanisms to distract and relax: • e.g. Interaction with virtual pet, breathing exercises (blowing into microphone)
Feedback Providing praise and feedback to the child and information for healthcare professionals to better guide management: • Track growth — predicted height • Technical issues with GH administration — e.g. capture feedback on bruising etc., record sound to assess duration of administration etc. • Adverse events

Acknowledgments: Strategen Limited provided editorial support to the authors funded by Ferring Pharmaceuticals.

Author Contributions: All the authors contributed to the evaluation of the relevant literature and drafting, critical review and approval of the final manuscript.

Research Funding: None declared.

Employment or leadership: KP is an employee of Ferring Pharmaceuticals, the manufacturer of Zomacton™ (somatropin [rDNA origin]).

Honorarium: None declared.

Competing interests: None declared.

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