8-2021

Innovative Computational Methods for Pharmaceutical Problem Solving a Review Part II: Serious Gaming

Heather R. Campbell
University of Kentucky, hrca227@gmail.com

Robert A. Lodder
University of Kentucky, lodder@g.uky.edu

Innovative Computational Methods for Pharmaceutical Problem Solving a Review Part II: Serious Gaming

Innovative Computational Methods for Pharmaceutical Problem Solving a Review Part II: Serious Gaming

Heather R Campbell and Robert A Lodder*

Department of Pharmaceutical Sciences, College of Pharmacy
University of Kentucky
Lexington, KY 40536
*Author to whom correspondence should be addressed. Lodder @ g.uky.edu

Abstract

Serious gaming has begun to take a foothold in pharmaceutical problem-solving. Companies such as Akili's Interactive are seeing success in the form of positive clinical trial results and FDA approval of digital therapeutics. Academic researchers have begun exploring novel uses for serious gaming in the way of protein design and more with promising results. This paper provides a review of such topics in addition to topics of game repurposing- repurposing a game originally intended for entertainment into a serious game-such as Minecraft and America's Army. Reviewing these topics this paper shows the utility of serious gaming as a tool for problem-solving while empathizing its applications in the pharmaceutical industry. Further, serious gaming's utility in other sectors is briefly discussed before concluding. It is suggested that serious games will be a powerful scientific tool both in terms of educational, training, and therapeutic purposes moving forward.

Keyword*: Serious game, applied gaming, video game therapies, game theory, pharmaceuticals*

I. Introduction

Serious gaming or applied gaming are games not used solely for entertainment but alternative purposes, such as educating or solving scientific problems. Though the origins of serious games are in defense or militaristic applications, not scientific problem-solving. For example, America's Army, released in 2002, soon became a recruitment and even supplement rifle training tool for the military (Zyda, 2005). However, thoughts on games' relationship with human behavior date back beyond digital games to philosophers such as Plato of the 4th Century BCE (Wilkinson, 2016). During this time, Plato theorized that reinforcing certain behaviors in children's play would reinforce those behaviors as an adult (D'Angour, 2013; Wilkinson, 2016). Plato's thoughts began a debate on the purpose of play and games' applications, with most believing that play was only for children and absence of a meaningful purpose. It was not until Friedrich Schiller, and Jean-Jacques Rousseau introduced their ideas that play started to be considered a meaningful activity (Bentley, 2009; Wilkinson, 2016). Indeed, Rousseau's story of

ISSN: 1547-8890

the hunters would later develop into SH, a standard game of game theory (Skyrms and Irvine, 2001). Although it took until the 18th Century to begin swaying the general opinions of play as an activity of purpose, it didn't stop some from at least metaphorically relating games to real-world problems. For example, in the 7th Century Chaturanga, an ancestor to Chess, is on record as being explicitly applied as a militaristic metaphor. Even its design seems to be of military origin (Smith, 2010; Wilkinson, 2016). Studies of strategic thinking games such as Chaturanga and Chess led to the development of Kriegspiel- a serious game similar to Chess that aimed to simulate war (Favini, 2010). Kriegspiel was developed by the Prussian military and is thought to have been an essential instrument for the army. The game is also on record as being used by the Japanese navy in the Russo-Japanese war of 1904-1905 (Favini, 2010). Kriegspiel's success in gaming war led to creations such as the RAND Corporation by the US Air Force. Since RAND's inception, the corporation has developed games and models for world events such as the Cold War competition and nuclear warfare (Hournshell, 1997). In addition to the RAND Corporations' work on militaristic applications, work has also been conducted with medical applications, as demonstrated by the collaboration between RAND and the University of Pittsburgh School of Medicine (Mohan et al., 2018, 2014). In these studies, researchers used serious games to investigate cognitive loads' influence on physician decision-making by measuring trauma triage and transfer decisions. Splitting physicians into different load groups, the researchers found that those physicians who finished the study made decisions consistent with actual practice and that cognitive load could be manipulated in-game. Further, the results aligned with the cognitive theory predictions that state-when cognitive load increases, the use of heuristics increase (Mohan et al., 2014). Scaling this study to 320 physicians working at non-trauma centers in the United States, the researchers hoped to improve physicians' heuristics through game interventions. Although suffering data corruption, among other limitations, the work did suggest that the game interventions reduced under triage cases digitally compared to a text-based intervention that did not (Mohan et al., 2018).

This paper will provide a comprehensive review of gaming as an innovative solution to pharmaceutical problems. Applications of serious gaming in the pharmaceutical industry will be discussed. Game-based therapeutics will be reviewed, including Akili's groundbreaking EndeavorRX, the first FDA-approved game therapy for treating attention deficit hyperactivity disorder (ADHD) (Mueller, 2020a). Further, this article will summarize advances due to gaming in other industries and provide input on future gaming directions in pharmaceutical sciences.

II. Serious/Applied Gaming by Definition

Serious gaming can be loosely defined as a game not used solely for entertainment. Serious games can draw from concepts of game theory, simulations, game design, and more to

solve or study complex problems. In scientific problem-solving, serious games are often used to create a controlled and observable environment that would otherwise be too difficult or too expensive to develop. Further, the games are generally in digital form but may take on other forms, such as board games and role-playing (Bolton, 2002). Serious games can be thought of as a participatory simulation and, when in digital format, as a virtually interactive simulation. The use of serious games can be found in industries such as engineering, defense, and healthcare (Meijer, 2012; Mohan et al., 2014; Naciri et al., 2012; Zyda, 2005). Further, serious games are considered a well-adapted tool for capturing human decision-making, allowing for quantitative or qualitative understanding of human decision-making behaviors. Unlike other data collection tools for human decision-making, such as questionnaires and interviews, serious games do not require an explicit description of the individual's actions and decisions. Instead, actions are captured, bypassing individuals' frequent inability to explain their own actions (Naciri et al., 2012). Further, serious games bypass potential bias found in question development and interviewer interpretation errors. However, serious games can be significantly longer and more expensive to develop. Hence, researchers must take care when choosing to utilize serious games. Serious games can quickly become expensive and time-consuming to develop. Hence, it is crucial to understand what makes a game when conceptualizing and developing a serious game. For example, game mechanics, elements, and metrics should be considered while balancing the game's entertainment aspect. Where game mechanics can be thought of as the rules and procedures that guide the player and the game's response to the player's actions (Boller, 2013a). Game metrics allow each player's behavior to be characterized quantitatively, and game elements or features are what keep players engaged (Boller, 2013b). Another often overlooked aspect of serious gaming development is understanding the relevance between game theory and serious games, as it may be challenging to grasp. It is important to note that not all serious games invoke game theory concepts, but when they do, the game can be significantly enhanced (Roungas et al., 2019).

The Beer Game is used to study optimization problems in complex networks and has been greatly enhanced by its game theory roots (Sterman, 1989; Thompson and Badizadegan, 2015). Game theory can be thought of as the mathematical approach of analyzing calculated circumstances in which a person's success is based upon others' choices (Meijer, 2012). That is, game theory concerns itself with developing mathematical models to determine the best strategies for rational agents under a given set of conditions. This approach in practice utilizes computer simulations and behavioral experiments, such as those detailed in Hauser's work, to reach conclusions on behavioral predictions of given scenarios (Hauser et al., 2019). On the other hand, serious games are not necessarily focused on predicting the outcome through mathematics. Instead, the relationship between decision and consequences are often studied as they occur. Indeed, this methodology is strikingly similar to that used in behavioral game theory

ISSN: 1547-8890

(Camerer, 1997). So it is that game theory and serious games are intertwined in their focus on relationships between decisions and outcomes. However, the approach and methodologies can be considered different depending upon how the serious game is designed. Therefore, it is up to the game designer in the conception and development stages of the game rather to harness game theory concepts or not. Researchers should note that attempting to utilize game theory mathematics with serious games is not easy. The authors suggest (Roungas et al., 2019) for the interested reader.

III. Serious/Applied Gaming in the Pharmaceutical Arena

In 2019 the FDA co-sponsored a free video game to prevent smoking entitled One Leaves, playable on Xbox and PC. The development came as a part of the FCB's "The Real Cost" campaign that promotes an anti-smoking agenda and highlights that out of every four teens who smoke cigarettes, only one will escape the addiction (Muoio, 2019). The statistic is provocatively played out within the game—allowing only one player out of four to escape a horror-themed maze.

One Leaves' mission is to educate and scare its players from smoking cigarettes. Thereby, helping them avoid all the potential diseases that are linked to smoking. But serious gaming in health and pharmaceuticals, can be more than an educational tool. Indeed, serious gaming can be therapeutic as demonstrated by Akili's-EndeavorRx game. After successful clinical trials, EndeavorRx became the first FDA-approved gaming therapeutic for the treatment of ADHD in 2020 (Kollins et al., 2020; Mueller, 2020b). EndeavorRx is intended for children ages 8-12 years old, with primarily inattentive or combined-type ADHD. Clinical trials showed that children within this age range had improved attention function after playing EndeavorRx. Where the computer-based Tests of Variables of Attention was used to as the primary measurement tool (Pena, 2020). Unfortunately, the game did not come without side effects. Of those tested, 9.3% of the subject's experienced effects, such as frustration, headache, dizziness, emotional reaction, nausea, or aggression (Akili's Interactive, 2020a; Kollins et al., 2020). However, it is of the author's opinion that these side effects are minimal compared to pharmacotherapy, as demonstrated in Table 1. Indeed, the most severe potential side-effects when treating with EndeavorRx is eye strain or joint pain. Compared to Adderall which may induce seizures. Furthermore, common medications used to treat ADHD are schedule II compounds such as Adderall-meaning; the compounds are controlled substances and have a high potential for abuse. An additional plus for EndeavorRx is comparable (though slightly higher) prescription pricing.

EndeavorRx prescriptions are for 96 days (about 3 months). Patients are to play uninterrupted for 25-30 minutes daily (Akili's Interactive, 2020a). For insured patients, the cost of this treatment is $450 (about $150 a month). Uninsured patients can get company assistance

ISSN: 1547-8890

which lowers the cost to about $100 a month (Coey, 2021). Compared to pharmacotherapies such as Adderall XR which can run from $30-$70 for a 30-day supply* (Medical Security Card Company, 2021). Making a 96-day, Adderall XR prescription in the range of $96-$220 -a slightly cheaper option than EndeavorRx. However, as the company continues to grow, and the field of digital therapies matures these prices may decrease.

*Estimate based on pharmacy pricing near Lexington, KY. Range representative of discount only rates not insurance rates.

Table 1: Side effects among common ADHD medications compared to that of EndeavorRX the digital gaming therapeutic.

Brand name	EndeavorRX	*Adderall	*Vyvanse	*Focalin XR	Strattera
Generic name	None	Mixed amphetamine salt	Lisdexamfetamine	Extended-release dexmethylphenidate	Atomoxetine
Type	Digital therapeutic	Short-acting amphetamine stimulant	Long-acting amphetamine stimulant	Long-acting methylphenidate stimulants	Long-acting non-stimulant
Most common side effects among children and adolescents	Frustration, headache, dizziness, emotional reaction, nausea or aggression.	Loss of appetite, insomnia, abdominal pain, emotional lability, vomiting, nervousness, nausea, and fever.	Anorexia, anxiety, decreased appetite, decreased weight, diarrhea, dizziness, dry mouth, irritability, insomnia, nausea, upper abdominal pain, and vomiting.	Dyspepsia, decreased appetite, headache, and anxiety for pediatric patients and dry mouth, dyspepsia, headache, and anxiety.	Nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence
Additional side effects and cautions	Eye strain, joint pain	Seizures, eyesight change, blurred vision, serotonin syndrome, possible slowing of growth, agitation, hallucinations, coma or other changes in mental status, muscle twitching, diarrhea.	Rash, pyrexia, somnolence, hyperhidrosis, erectile dysfunction, decreased libido	Vomiting, gastrointestinal disorders, insomnia, libido changes	Irritability, anorexia, headache, dizziness, depression, insomnia, weight decrease.

ISSN: 1547-8890

*Schedule II compound.This table is not intended to be treated as all encompassing. Information for this table was found at (Akili's Interactive, 2020a, 2020b; American Academy of Pediatrics, 2019; Division of Teva Pharmaceuticals USA, 2017; Eli Lilly and Company, 2009; Kollins et al., 2020; Novartis Pharmaceuticals Corporation, 2017; Shire US Inc., 2015).

EndeavorRx is the first FDA-approved digital therapeutic of what seems to be many more to come given Akili's Interactive and their competitors continue to work on gaming treatments for other common disorders. Indeed, at the time of authoring this paper, Akili's Interactive is continuing pilot studies for three potential digital therapeutics AKL-T02, AKL-T03, and AKL-T04. AKL-T02 being a possible digital treatment for attention symptoms in children with an autism spectrum disorder (Yerys et al., 2019). AKL-T03 and AKL-T04 are potential digital treatments of cognitive deficiencies in adults who suffer from major depression (Akili's Interactive, 2020a). In addition, AKL-T03 is also undergoing feasibility studies as a potential treatment for cognitive impairment in patients with multiple sclerosis (Bove et al., 2019). Grendel Games, a Dutch serious gaming company, has not received FDA approval for their digital treatment Gryphon Rider. Regardless, the game was specifically designed to aid young children recovering from acquired brain injury (Grendel Game, 2014). Specifically the game is designed to motivate children when repetitive rehabilitation exercises are needed. Children can play Gryphon Rider by moving their bodies as the game allows you to take the reins of a gryphon (or griffin)- a mythological creature with the body of a lion and head and wings of an eagle- and navigate various worlds. Further, game designers have also developed games for improved health.

Dr. Jane McGonigal, a game designer who advocates for technology to channel positive attitudes and collaboration, developed the serious game SuperBetter. SuperBetter aims to improve mental health and resilience in its players, with promising results in randomized control studies (Roepke et al., 2015). Furthermore, SuperBetter has seen promising clinical trial results as a gaming intervention to reduce concussion symptoms in teenagers (Worthen-Chaudhari et al., 2017). Researchers have also gotten in on the fun of developing health-improving games. Serious gaming therapies have also gained popularity among academic researchers such as Lodder and Titto's work through game repurposing the popular console and PC game-Minecraft (Lodder et al., 2017; Lodder and Tiitto, 2017). In these studies, Lodder's group developed specially designed training activities performed within Minecraft to determine if they affected executive function, working memory, or restraint in patients diagnosed with ADHD (Id et al., 2017). After a promising feasibility study, the digital treatment moved into clinical trials when at the time of writing is still in the recruitment phase (Lodder and Tiitto, 2017; Tiitto, 2019). Rehabilitation of the upper extremities for stroke patients through gaming has also being explored (Yates et al., 2016). Where Yates claims that the literature seems promising for the use of virtual reality games as rehab therapies for stroke patients. Further, Yates' found support that

these gaming therapies can be equivalent to traditional therapies or at least act as a good addition to a patient's current treatment plans (Yates et al., 2016). Researchers have also attempted to use serious gaming concerning vaccines.

Although an effective and proven method of preventing infectious diseases, vaccination has faced hesitancy by the public largely due to a retracted paper linking autism and the measles, mumps, and rubella vaccine (Rao and Andrade, 2011). Since the release of that paper in 1998, researchers and public agencies have attempted to improve public opinions towards vaccines. Over two decades later, doubt of vaccines' efficacy and utility still exist. It is here where researchers are hoping serious gaming can be helpful to vaccines. It is thought that by implementing vaccine information into serious games, the games can act as an innovative educational tool for public health (Ohannessian et al., 2016). For example, Tiltfactor laboratories' POX: Save the People (Flanagan et al., 2011). A serious game that explores anti-vaccination movement consequences and educates the player on herd immunity and the need to vaccinate. Some researchers believe that serious gaming can be more than just a tool to improve public opinion but as a vaccine itself. Dennis D. Embry's work on making the Good Behavioral Game a universal behavioral vaccine is one example (Embry, 2002). In addition to serious games' potential as a disease prevention tool or therapy, serious games have also found utility throughout the DDP.

Games have found utility throughout the DDP. For example, Foldit, an online puzzle game about protein folding, has led to several scientific breakthroughs by harassing community science in a game. In 2010, Foldit provided insights that solved the crystal structure of M-PMV retroviral protease, an enzyme involved in reproducing HIV in just three weeks (Khatib et al., 2010). In 2011, Foldit players developed an energy optimization algorithm for protein folding that had significant similarities to the unpublished algorithm scientists had been developing for years (Khatib et al., 2011). These algorithms showed considerable improvement compared to the benchmark algorithm Classic Relax used within the Rosetta structure prediction and design program. The scientist developed algorithm- Fast Relax, went on to be implemented into all Rosetta de novo and homology modeling methods. In addition to these discoveries, Foldit monomer design puzzles have also led researchers to develop a potential new approach for designing proteins (Foldit Staff, 2020). In light of the COVID-19 pandemic, researchers were also attempting to use Foldit to discover a protein to bind to the interleukin receptor to treat the cytokine storm found in advanced COVID-19 patients.

In the next section examples of serious gaming in other industries is provided.

ISSN: 1547-8890

IV. Gaming in other Industries

The world of technology, including technology transfer and cybersecurity, has also gained insights from gaming (Henry et al., 2017; Kumar and Bhuyan, 2019). RAND Corporations' serious game 360 was initially created to address the Defense Advanced Research Projects Agency (DARPA) challenges with technology transfer. 360's capabilities and success allowed for its use in other endeavors, such as successfully being applied to develop a cybersecurity framework for the Hewlett Foundation (Henry et al., 2017). The objective-driven game brings together stakeholders, subject-matter experts, and hands-on operators to reveal solutions to target problems. Between 30-60, players are split into groups to solve smaller elements of the larger target problem. Pinning players against a scenario, the game is intended to provide necessary insights for decision-makers when other analytical tools cannot be leveraged (Henry et al., 2017). Politics and policy have also been simulated in serious games, although typically for educational rather than problem-solving purposes.

The political game Peacemaker by Impact Games educates players on conflict resolution by challenging its players to bring peace between Israeli and Palestinian conflict (Impact Game Staff, 2020). This is done by casting players as either the Israeli Prime Minister or the Palestinian President. Once cast a role, players are presented real news footage and images for events occurring in the Middle East that the player must make decisions on. A Force More Powerful, documentary turned serious game is another example of political education through gaming (Staff, 2006). The game released in 2006 was co-produced by The International Center on Nonviolent Conflict (ICNC), and York Zimmerman Inc set out to teach players nonviolent strategies to overcome real-world adversaries (e.g., corrupt rulers). Although no longer supported the game's sequel, People Power: The Game of Civil Resistance has a similar goal and is still actively supported (MAROVIC et al., 2015). Another noteworthy serious game is IBM's IBM City One, a city-building simulation designed to help IBM clients understand the potential of innovative and sustainable solutions in areas of energy, water, retail, and banking (Grant, 2010). The game released in 2010 provides a venue for policymakers and regulators to explore solutions that can be implemented into their daily work by placing players in charge of realistic city development decisions. Players start with one of the four industries and eventually move into all four while considering the city's revenue, profit, citizen satisfaction, and environmental betterment. As the player progresses, a series of crisis scenarios are presented that force the player to balance economic, ecological, and sociological concerns. In making their decisions, players can then explore the consequences of innovative and sustainable solutions through the game that would otherwise be too difficult and costly to explore.

ISSN: 1547-8890

V. Conclusions

Serious gaming has begun to take a foothold in pharmaceutical problem-solving. Companies such as Akili's Interactive are now starting to see success in the form of clinical trials and FDA approval for digital therapeutics. Academic researchers have begun exploring novel uses for serious gaming in the way of protein design and more with promising results. Additionally, game repurposing- repurposing a game originally intended for entertainment into a serious game-has been explored in games such as Minecraft and America's Army also with promising results. Other possible games with repurposing potential are games such as BigPharma by Twice Circled and Klabater, which immerse players into a realistic and decision-making pharmaceutical environment and can be easily modified. Regardless of the method used rather through novel development or game repurposing, serious gaming applications can only expand as the gaming industry grows, and U.S. universities begin opening serious and esport gaming departments. This paper has shown the utility of serious gaming as a tool for problem-solving while empathizing its applications in the pharmaceutical industry. A review of serious gaming as a digital treatment has been provided along with serious gaming applications in other sectors.

VI. Acknowledgements

We would like to acknowledge the Department of Pharmaceutical Sciences at the University of Kentucky for financial support. The project described was supported in part by the NIH National Center for Advancing Translational Sciences through grant number UL1TR001998. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

VII. References

Akili's Interactive, 2020a. Endeavor: Instructions for use.

Akili's Interactive, 2020b. Introducing the future of medicine , today . EndeavorRx has been evaluated in over 600 children with ADHD across EndeavorRx is part of the EndeavorRx Treatment System ™ care program that gives you : [WWW Document]. Akili Interact. Labs, Inc.

American Academy of Pediatrics, 2019. Common ADHD Medications & Treatments for Children - HealthyChildren.org [WWW Document]. Am. Acad. Pediatr. URL https://www.healthychildren.org/English/health-issues/conditions/adhd/Pages/Determining-ADHD-Medication-Treatments.aspx

Bentley, S.M., 2009. Friedrich Schiller's play: A theory of human nature in the context of the eighteenth-century study of life, University of Louisville Electronic Theses and Dissertations. https://doi.org/10.18297/etd/101

Boller, S., 2013a. Learning Game Design: Game Elements [WWW Document]. TiER1 Perform. URL http://www.theknowledgeguru.com/learning-game-design-game-elements/

Boller, S., 2013b. Learning Game Design : Game Mechanics [WWW Document]. TiER1 Perform.

Bolton, G.E., 2002. Game theory's role in role-playing. Int. J. Forecast. 18, 353–358.

Bove, R.M., Rush, G., Zhao, C., Rowles, W., Garcha, P., Morrissey, J., Schembri, A., Alailima, T., Langdon, D., Possin, K., Gazzaley, A., Feinstein, A., Anguera, J., 2019. A Videogame-Based Digital Therapeutic to Improve Processing Speed in People with Multiple Sclerosis: A Feasibility Study. Neurol. Ther. 8, 135–145. https://doi.org/10.1007/s40120-018-0121-0

Camerer, C.F., 1997. Progress in behavioral game theory. J. ofE Con. Perspect. 11, 167–188.

Coey, S.K., 2021. It ' s game on for Akili as it launches digital campaign for first FDA-approved ADHD video game [WWW Document]. Fierce Pharma.

D'Angour, A., 2013. Plato and Play: Taking Education Seriously in Ancient Greece. Am. J. Play 5, 293–307.

Division of Teva Pharmaceuticals USA, 2017. Adderall Medication Guide.

Eli Lilly and Company, 2009. Strattera Medicine Guide.

Embry, D.D., 2002. The Good Behavior Game: A best practice candidate as a universal behavioral vaccine. Clin. Child Fam. Psychol. Rev. 5, 273–297. https://doi.org/10.1023/A:1020977107086

Favini, G.P., 2010. The dark side of the board: advances in chess Kriegspiel, University of Bologna.

Flanagan, M., Seidman, M., Belman, J., Punjasthitkul, S., Downs, Z., Ayoob, M., Driscoll, A., Downs, M., 2011. Preventing a POX among the people? A design case study of a public health game. Proc. DiGRA 2011 Conf. Think Des. Play.

Foldit Staff, 2020. Foldit Solve Puzzles for Science [WWW Document]. UW Cent. Game Sci. UW Inst. Protein Des. Northeast. Univ. Vanderbilt Univ. Meiler Lab, UC Davis. URL https://fold.it/portal/node/2010013

Grant, S., 2010. IBM CityOne [WWW Document]. Serious Games Work. URL http://www-01.ibm.com/software/solutions/soa/innov8/cityone/

Grendel Game, 2014. Gryphon Rider [WWW Document]. URL https://grendelgames.com/game/gryphon-rider/

Hauser, O.P., Hilbe, C., Chatterjee, K., Nowak, M.A., 2019. Social dilemmas among unequals. Nature 572, 524–527. https://doi.org/10.1038/s41586-019-1488-5

Henry, R., Berner, S., Shlapak, D.A., 2017. Serious Analytical Gaming: The 360 Game for Multidimensional Analysis of Complex Problems.

Hournshell, D., 1997. The Cold War, RAND, and the Generation of Knowledge, 1946-1962, in: Historical Studies in the Physical and Biological Sciences. pp. 237–267.

Id, A., Author, N.C., Lodder, R., Sciences, P., Complex, B., States, U., Author, A.S., Lodder, R., Sciences, P., Complex, B., States, U., Authors, A.O., Tiitto, M., Sciences, P., States, U., 2017. Therapeutic Video Games for Attention Deficit Hyperactivity Disorder (ADHD) Therapeutic Video Games for Attention Deficit Hyperactivity Disorder (ADHD) Videogames 1–9.

Impact Game Staff, 2020. Peacemaker [WWW Document]. Impact Games. URL http://d0x3d.com/d0x3d/get_the_game.html

Khatib, F., Cooper, S., Tyka, M.D., Xu, K., Makedon, I., Popović, Z., Baker, D., Players, F., 2011. Algorithm discovery by protein folding game players. Proc. Natl. Acad. Sci. U. S. A. 108, 18949–18953. https://doi.org/10.1073/pnas.1115898108

Khatib, F., Dimaio, F., Cooper, S., Kazmierczyk, M., Gilski, M., Krzywda, S., Zabranska, H., Pichova, I., Thompson, J., Popović, Z., Jaskolski, M., Baker, D., 2010. Crystal structure of a

monomeric retroviral protease solved by protein folding game players. Nat. Struct. Mol. Biol. 18, 1175–1177. https://doi.org/10.1038/nsmb.2119

Kollins, S.H., DeLoss, D.J., Cañadas, E., Lutz, J., Findling, R.L., Keefe, R.S.E., Epstein, J.N., Cutler, A.J., Faraone, S. V., 2020. A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): a randomised controlled trial. Lancet Digit. Heal. 2, e168–e178. https://doi.org/10.1016/S2589-7500(20)30017-0

Kumar, B., Bhuyan, B., 2019. Using game theory to model DoS attack and defence. Sadhana - Acad. Proc. Eng. Sci. 44. https://doi.org/10.1007/s12046-019-1228-4

Lodder, R., Tiitto, M., 2017. Therapeutic Video Games for Attention Deficit Hyperactivity Disorder (ADHD). WebmedCentral Paediatr. 8, 1–9.

Lodder, R., Tiitto, M., Smith, R., Banfield, A., Ensor, M., 2017. A Pilot Study of a Device and Drug Therapy for ADHD. WebmedCentral Paediatr. 8, 1–25.

Marovic, I., Maka, C., Sherbrooke, A., Palumbo, A., Turner, R., Blechman, B., Morgan, T., Green, H., Traynham, D., Watmough, J., Pulecio, A., Jung, T., Johnson, B., Sherbrooke, A., Lizardi-sullivan, D., Zimmerman, M., York, S., 2015. People Power [Www Document]. York Zimmerman Inc Int. Cent. Nonviol. Confl.

Medical Security Card Company, 2021. Dextroamphentamine Generic Pricing in Near Lexington, KY [WWW Document]. ScriptSaver WellRx.

Meijer, S., 2012. Gaming Simulations for Railways: Lessons Learned from Modeling Six Games for the Dutch Infrastructure Management, in: Infrastructure Design, Signalling and Security in Railway. https://doi.org/10.5772/35864

Mohan, D., Angus, D.C., Ricketts, D., Farris, C., Fischhoff, B., Rosengart, M.R., Yealy, D.M., Barnato, A.E., 2014. Assessing the validity of using serious game technology to analyze physician decision making. PLoS One 9. https://doi.org/10.1371/journal.pone.0105445

Mohan, D., Fischhoff, B., Angus, D.C., Rosengart, M.R., Wallace, D.J., Yealy, D.M., Farris, C., Chang, C.C.H., Kerti, S., Barnato, A.E., 2018. Serious games may improve physician heuristics in trauma triage. Proc. Natl. Acad. Sci. U. S. A. 115, 9204–9209. https://doi.org/10.1073/pnas.1805450115

Mueller, N., 2020a. FDA Permits Marketing of First Game-Based Digital Therapeutic to Improve Attention Function in Children with ADHD [WWW Document]. Food Drug Adm. FDA. URL https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-game-based-digital-therapeutic-improve-attention-function-children-adhd

Mueller, N., 2020b. FDA Permits Marketing of First Game- Based Digital Therapeutic to Improve Attention Function in Children with ADHD [WWW Document]. U.S. Food Drug Adm. URL https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-first-game-based-digital-therapeutic-improve-attention-function-children-adhd

Muoio, D., 2019. FDA co-sponsors horror video game to scare teens away from cigarettes [WWW Document]. mobihealthnews. URL https://www.mobihealthnews.com/content/fda-co-sponsors-horror-video-game-scare-teens-away-cigarettes

Naciri, S., Yoo, M.J., Glardon, R., 2012. Using serious games for collecting and modeling human procurement decisions in a supply chain context, in: Handbook of Research on Serious Games as Educational, Business and Research Tools. pp. 135–156. https://doi.org/10.4018/978-1-4666-0149-9.ch007

Novartis Pharmaceuticals Corporation, 2017. Focalin XR.

ISSN: 1547-8890

Ohannessian, R., Yaghobian, S., Verger, P., Vanhems, P., 2016. A systematic review of serious video games used for vaccination. Vaccine 34, 4478–4483. https://doi.org/10.1016/j.vaccine.2016.07.048

Pena, C., 2020. Endeavor's FDA Approval Letter. Dk. https://doi.org/10.1017/CBO9781107415324.004

Rao, T.S.S., Andrade, C., 2011. The MMR vaccine and autism: Sensation, refutation, retraction, and fraud. Indian J. Psychiatry 53, 95–96. https://doi.org/10.4103/0019-5545.82529

Roepke, A.M., Jaffee, S.R., Riffle, O.M., McGonigal, J., Broome, R., Maxwell, B., 2015. Randomized Controlled Trial of SuperBetter, a Smartphone-Based/Internet-Based Self-Help Tool to Reduce Depressive Symptoms. Games Health J. 4, 235–246. https://doi.org/10.1089/g4h.2014.0046

Roungas, B., Bekius, F., Meijer, S., 2019. The Game Between Game Theory and Gaming Simulations: Design Choices. Simul. Gaming 50, 180–201. https://doi.org/10.1177/1046878119827625

Shire US Inc., 2015. Vyvanse Medication Guide.

Skyrms, B., Irvine, U.C., 2001. The Stag Hunt. Proc. Addresses Am. Philos. Assoc. 75, 31. https://doi.org/10.2307/3218711

Smith, R., 2010. The long history of gaming in military training. Simul. Gaming 41, 6–19. https://doi.org/10.1177/1046878109334330

Staff, I., 2006. A Force More Powerful: The Game of Nonviolent Strategy [WWW Document]. Int. Cent. Nonviol. Confl. (ICNC), York Zimmerman Inc.,.

Sterman, J.D., 1989. Modeling Managerial Behavior: Misperceptions of Feedback in a Dynamic Decision Making Experiment. Manage. Sci. 35, 321–339. https://doi.org/10.1287/mnsc.35.3.321

Thompson, K.M., Badizadegan, N.D., 2015. Valuing information in complex systems: An integrated analytical approach to achieve optimal performance in the beer distribution game. IEEE Access 3, 2677–2686. https://doi.org/10.1109/ACCESS.2015.2505730

Tiitto, M., 2019. Therapeutic Video Games and the Simulation of Executive Function Deficits in Adhd.

Wilkinson, P., 2016. A Brief History of Serious Games. Entertain. Comput. Serious Games 9970, 17–41. https://doi.org/10.1007/978-3-319-46152-6

Worthen-Chaudhari, L., McGonigal, J., Logan, K., Bockbrader, M.A., Yeates, K.O., Mysiw, W.J., 2017. Reducing concussion symptoms among teenage youth: Evaluation of a mobile health app. Brain Inj. 31, 1279–1286. https://doi.org/10.1080/02699052.2017.1332388

Yates, M., Kelemen, A., Sik Lanyi, C., 2016. Virtual reality gaming in the rehabilitation of the upper extremities post-stroke. Brain Inj. 30, 855–863. https://doi.org/10.3109/02699052.2016.1144146

Yerys, B.E., Bertollo, J.R., Kenworthy, L., Dawson, G., Marco, E.J., Schultz, R.T., Sikich, L., 2019. Brief Report: Pilot Study of a Novel Interactive Digital Treatment to Improve Cognitive Control in Children with Autism Spectrum Disorder and Co-occurring ADHD Symptoms. J. Autism Dev. Disord. 49, 1727–1737. https://doi.org/10.1007/s10803-018-3856-7

Zyda, M., 2005. From Virtual Simulation to Virtual Reality to Games. IEEE Comput. Soc. 25–32.

ISSN: 1547-8890

ISSN: 1547-8890