ARTICLE

A Video Game Improves Behavioral Outcomes in Adolescents and Young Adults With Cancer: A Randomized Trial

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What's Known on This Subject

Adherence is a significant problem when managing chronic illness. There is some evidence that video games and/or interactive multimedia tools can help to improve health-related behaviors in pediatric populations, but conclusions from these studies have been tentative because of small study size and inadequate controls.

What This Study Adds

To our knowledge, this is the first large-scale, randomized, intervention trial, pharmaceutical or behavioral, conducted with a study population composed exclusively of AYA with cancer. The intervention focuses on treatment adherence, a pervasive problem in this age group in general.

ABSTRACT

OBJECTIVE. Suboptimal adherence to self-administered medications is a common problem. The purpose of this study was to determine the effectiveness of a video-game intervention for improving adherence and other behavioral outcomes for adolescents and young adults with malignancies including acute leukemia, lymphoma, and soft-tissue sarcoma.

METHODS. A randomized trial with baseline and 1- and 3-month assessments was conducted from 2004 to 2005 at 34 medical centers in the United States, Canada, and Australia. A total of 375 male and female patients who were 13 to 29 years old, had an initial or relapse diagnosis of a malignancy, and currently undergoing treatment and expected to continue treatment for at least 4 months from baseline assessment were randomly assigned to the intervention or control group. The intervention was a video game that addressed issues of cancer treatment and care for teenagers and young adults. Outcome measures included adherence, self-efficacy, knowledge, control, stress, and quality of life. For patients who were prescribed prophylactic antibiotics, adherence to trimethoprim-sulfamethoxazole was tracked by electronic pill-monitoring devices ($n = 200$). Adherence to 6-mercaptopurine was assessed through serum metabolite assays ($n = 54$).

RESULTS. Adherence to trimethoprim-sulfamethoxazole and 6-mercaptopurine was greater in the intervention group. Self-efficacy and knowledge also increased in the intervention group compared with the control group. The intervention did not affect self-report measures of adherence, stress, control, or quality of life.

CONCLUSIONS. The video-game intervention significantly improved treatment adherence and indicators of cancer-related self-efficacy and knowledge in adolescents and young adults who were undergoing cancer therapy. The findings support current efforts to develop effective video-game interventions for education and training in health care. *Pediatrics* 2008;122:e305–e317

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Key Words

adherence, cancer, video game, adolescent, pediatric oncology, randomized trial

Abbreviations

AYA—adolescents and young adults
6-MP—6-mercaptopurine
TMP/SMX—trimethoprim-sulfamethoxazole
6MMP—methylmercaptopurine nucleotides
6-TG—6-thioguanine nucleotides
MEMS—Medication Event Monitoring System
CDCI—Chronic Disease Compliance Instrument

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PATIENT NONADHERENCE TO treatment regimens is an ongoing problem in the practice of medicine in general.[1] It is widely known that adolescents and young adults (AYA) with cancer often fail to adhere to prescribed treatment regimens, especially self-administered treatments such as oral chemotherapy.[2–7] This is a significant challenge to overcome especially in light of the fact that cancer incidence for AYA has increased over time to become the leading cause of nonaccidental death in this age group.[8,9] Development of effective treatment protocols in the past 2 decades has dramatically reduced childhood cancer mortality rates, but AYA have not shown comparable benefits.[9] Suboptimal treatment adherence is believed to contribute to this disparity.[10–14] Intensive behavioral interventions involving

1-on-1 instruction and nurse home visits have been shown to increase adherence[15] and affect survival among patients with cancer.[16] A more efficient and easily distributed adherence intervention targeted to the needs of this particular patient population may hold promise for improving clinical disease outcomes in this group and provide a model for addressing noncompliance in other disease groups as well.

Several cognitive and motivational processes are hypothesized to affect treatment adherence, including knowledge about the therapy and its relationship to health,[2,13,17,18] perceptions of one's ability to influence health outcomes (perceived control),[19,20] and confidence in one's ability to meet the specific demands of cancer treatment and recovery (cancer-specific self-efficacy).[21–24] Previous interventions have sought to affect these psychological determinants of patient behavior by using traditional didactic learning strategies. The approach explored in this study exploits new opportunities for learning and improving health outcomes through video-game technology.

Video games may provide several advantages over didactic teaching as tools for affecting health behaviors, including vicarious practice of target skills, complex problem-solving, contingency-based learning of targeted information, and procedural knowledge in an interactive format.[25–27] Conventional video games have been used as intervention tools for health mostly as a means of distraction for pain.[28] Video-game–based interventions have been specifically developed for asthma,[27,29,30] diabetes,[31–33] cystic fibrosis,[34] and cancer.[35,36] Clinical studies have linked game use to indicators of effective disease management, including blood glucose levels,[37] self-care behaviors,[33,37] symptom management,[29] self-efficacy,[27] disease-related knowledge,[27,29,34] and emergency department use.[29] Conclusions from these studies are suggestive but tentative because of small study size and inadequate controls (with some exceptions[29,33,34]).

On the basis of theories of video-game–based learning and suggestive evidence that video games can improve health-related behavior in other contexts, we developed a video game for AYA with cancer. Behavioral objectives were translated into game structure on the basis of principles from the self-regulation model of health and illness,[38–42] social cognitive theory,[43] and learning theory.[44–46] We report the results from a multicenter, randomized trial that tested the efficacy of this intervention to improve adherence to prescribed treatment regimens and other health-related behavioral outcomes in AYA who were undergoing active treatment for cancer.

METHODS

Participants

Patients were recruited by fliers and staff contact at 34 academic medical centers and community practices in the United States, Canada, and Australia. Participation was open to patients who were aged 13 to 29 years and had a malignancy diagnosis (newly diagnosed or relapsed) and were undergoing treatment (chemotherapy, radiation, or stem cell transplantation) that was expected to last at least 4 months after enrollment. Exclusion criteria were a history of seizures as a result of photosensitivity (eg, flashing lights); inability to communicate with study personnel in English, French, or Spanish; or inability to follow the study schedule or directions.

Written informed consent was obtained from adult participants or from a minor's parent or legal guardian. Information on race/ethnicity was provided by patient self-report. All procedures were approved by local institutional review boards.

Study Design

This 2-arm randomized trial assessed the incremental effect of playing the cancer-targeted video-game intervention over and above any general effect of playing a video game. After baseline assessment, all participants received a Shuttle SB51G mini-computer (Shuttle, Inc, Taiwan) that contained a commercial game alone (control group) or the same commercial game plus the intervention game (intervention group). Participants were asked to play the game(s) for at least 1 hour per week during the 3-month study period, and serial outcome assessments were collected at 1 and 3 months after baseline. Game use was recorded electronically, and computers were retrieved after study completion.

Randomization

After baseline assessments, a site associate contacted a study coordinator at a central office, who gave the associate a number indicating a specific computer to be distributed to the participant (ie, a computer implementing the control or experimental condition). Computer allocation was randomized within sites (as blocks) on the basis of a computerized random-number generator. Condition assignment of each participant was concealed from study personnel, but participants became aware of their treatment assignment once they logged onto their assigned computers.

The Intervention Game

Re-Mission[47] (www.re-mission.net) is a PC game in which players control a nanobot, "Roxxi," in 3-dimensional environments within the bodies of young patients with cancers that commonly are diagnosed in AYA (acute lymphoblastic leukemia, acute myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, osteosarcoma, Ewing sarcoma, and brain tumors). Game content was engineered to address behavioral issues that were identified in literature reviews and preproduction targeting studies[48–54] as critical for optimal AYA patient participation in cancer treatment. Video-game play includes destroying cancer cells and managing common treatment-related adverse effects such as bacterial infections, nausea, and constipation by using chemotherapy, antibiotics, antiemetics, and a stool softener as ammunition. To win, players control the nanobot, Roxxi, to ensure strategically that virtual patients engage in positive self-care behaviors, such as taking oral chemotherapy to fight cancer cells, taking antibiotics to fight infection, taking stool soft-

TABLE 1 **Description of Measures of Primary and Secondary End Points**

Measures	Type of Measure	Description	Cronbach's α[a]
Primary end points			
CDCI[57]	Self-report	A measure of adherence to medical treatment of young people with cancer, translated and adapted from the original Finnish version of the scale.[56,57] On this 18-item scale, responses are rated on a scale from 1 to 5, and total scores range from 18 to 90.	.83
MAS[58]	Self-report	A measure of general adherence to medical treatment. This is a 4-item scale with yes/no questions; scores range from 0 to 4 with higher scores representing greater adherence.	.57
Clinic Visit Attendance	Objective	Scores reflect percentage of clinic visits missed as tracked by study associates.	NA
MEMS[59,60]	Objective	A measure of adherence to TMP/SMX (Septra, Bactrim, cotrimoxazole) for patients prescribed this drug for antimicrobial prophylaxis. The MEMS consists of a medication container with a cap that contains a microprocessor that records the dates and times the container is opened.	NA
6-MP blood assays	Objective	Blood metabolites of 6MMP and 6-TG provide an indication of adherence to 6-MP. Assays are performed on duplicate samples at a central laboratory with a standard high-performance liquid chromatography assay.[61]	NA
Secondary end points			
Self-efficacy Scale	Self-report	A measure of one's confidence in his or her ability to carry out specific behaviors to reach a goal according to Social Cognitive Theory.[62] This measure was constructed in accordance with the standard method for designing self-efficacy scales.[63,64] As such, it was designed specifically for this study to assess self-efficacy beliefs targeted in the intervention game. Responses on this 27-item scale are rated on a Likert scale of 1 to 7, where total scores reflect the average rating of all items (maximum score: 7) with higher scores indicating greater perceived self-efficacy to manage cancer and its treatment (see Appendix 1).	.93
Cancer Knowledge Scale	Self-report	Developed specifically for this study as a measure of patients' knowledge about cancer as delivered in the intervention game. In this 18-item multiple-choice questionnaire, total scores range from 0% to 100%, with higher scores indicating greater cancer-related knowledge (see Appendix 2).	NA
PQL—Generic Core Scale Version 4.0[65]	Self-report	A measure of physical and psychological quality of life of children aged 13–18. The 23 items on this scale are made up of 8 physical quality of life items and 15 psychological quality of life items. Items are rated on a scale of 0 to 4 and are transformed linearly to a 0 to 100 scale for scoring. Higher scores indicate a greater quality of life.	.91
FACT-G[66,67]	Self-report	A measure of the functional status of patients aged ≥18 with cancer. The 27 items are rated on a Likert scale of 0 to 4. The total FACT-G score is the summation of the 4 subscale scores and ranges from 0 to 108.	.92
Multidimensional Health Locus of Control Scale Form C[68]	Self-report	This 18-item scale is a measure of patients' perceptions of sources of control over their health. All items are rated on a scale of 1 to 6, and scores are calculated for 5 subscales that indicate the patient's perception of control in relation to different sources of influence (ie, self, chance, powerful others, doctors, other people). The total scores for the subscales range from 3 to 36, with higher scores indicating higher locus of control.	.56–.77
Perceived Stress Scale 10[69]	Self-report	This 10-item scale measures the degree to which situations in one's life are appraised as stressful. Items are rated on a scale of 1 to 5, and total scores range from 10 to 50 with higher scores indicating more stress.	.85

NA indicates not available; PQL, Pediatric Quality of Life Inventory; FACT-G, Functional Assessment of Cancer Therapy–General.

[a] Cronbach's α is an indicator of construct validity. Coefficients were calculated from baseline data in this sample.

eners to prevent bowel perforations, practicing good mouth care to combat mucositis, using relaxation techniques to reduce stress, and eating food to gain energy. Neither the nanobot nor any of the virtual patients "die" in the game. If players "fail" at any point in the game, then the nanobot powers down and players are given the opportunity to try the mission again. Players had to complete missions successfully before moving on to the next level.

The Commercial Game

A PC version of Indiana Jones and the Emperor's Tomb[55] served as the control game because the play structure and controller interface closely resembled that of Re-Mission.

Study End Points

The primary end point was adherence to prescribed cancer treatment regimen (including assessment of plasma 6-mercaptopurine [6-MP] metabolites by HPLC [Prometheus Laboratories, San Diego, CA] and Medication Event Monitoring System (MEMS)-cap electronic monitoring of trimethoprim-sulfamethoxazole [TMP/SMX] use [Aprex, San Diego, CA]). Secondary end points included self-efficacy to manage cancer, knowledge about cancer, health locus of control, stress, and quality of life. Self-report measures were available in English, Spanish, or Canadian French and translated when necessary. Standard procedures were used to translate these documents.[56] Table 1 describes each measure.

Statistical Methods

Sample size was estimated on the basis of a previous 38-patient pilot study conducted at Stanford University and the University of Texas Health Science Center at San Antonio. Analyses targeted detection of an effect size of

0.2 SD with 80% power and $\alpha = .05$ (2-sided), with adjustment for an anticipated 20% attrition rate.

Statistical analyses were conducted on an intention-to-treat basis using SAS 9.1.3 (SAS Institute, Inc, Cary, NC). Primary analyses used a repeated-measures mixed-effect linear model testing differences between treatment groups at 3 time points in a 2 (treatment) × 3 (time) factorial design (SAS PROC MIXED). Intervention effects on outcome trajectories over time were gauged by the treatment × time interaction term. Analyses that adjusted for effects of gender, age at study entry, and interval between entry and diagnosis (or relapse) did not alter primary conclusions (data not shown).

Primary analyses also adjusted for game system use by including an indicator variable ("anyplay": 1 = played the game(s) at least once; 0 = never played). The anyplay × treatment interaction term assessed whether treatment effects were greater for those who accessed the game system versus not at all.

TMP/SMX (MEMS) dose count data were analyzed using Poisson regression adjusting for individual differences in prescribed numbers of antibiotic doses (SAS PROC GENMOD).

Blood 6-MP metabolite values (methylmercaptopurine nucleotides [6MMP] and 6-thioguanine nucleotides [6-TG]) were log-transformed and analyzed using mixed-effect linear modeling as described. Observations that were conducted when participants were not scheduled to take 6-MP were excluded from analysis. Analyses examined 6MMP and 6-TG levels as separate indicators of 6-MP consumption (2 metabolite × 2 condition × 3 time analysis) and, alternatively, as the arithmetic sum of the 2 metabolites to estimate total 6-MP consumption.

To test the hypothesis that the effects of the intervention on primary outcomes (adherence) were mediated by changes in secondary outcomes (knowledge and/or self-efficacy), we conducted standard multivariate mediation analyses as previously described.[70] Mediation analyses of TMP/SMX adherence during 3 months of follow-up compared the effects of intervention condition on primary outcomes in an unmediated model with the effects observed in a mediated model that controlled for changes between baseline and the average of 1- and 3-month follow-up scores of the secondary outcomes (treated as mediators). As described,[70] mediation was indicated by a significant intervention effect in an unmediated model that changed to a nonsignificant intervention effect in a mediated model (ie, the residual significance of the intervention effect when controlling for candidate mediator). Similar mediation analyses were conducted for 6-MP metabolite levels, with the total effect of experimental conditions quantified by statistical significance of the condition × time interaction term as described, and the residual effect was quantified by the significance of the same interaction term after controlling for simultaneous changes in the value of a candidate mediator. The 2-degrees-of-freedom intervention condition × time interaction term simultaneously tests changes from baseline to 1-month follow-up and from baseline to 3-month follow-up while controlling for changes in the value of the mediator from baseline to 1-month follow-up and baseline to 3-month follow-up, respectively.[71]

RESULTS

Study Population

A total of 533 AYA with cancer were screened for study eligibility (Fig 1) from October 2004 to July 2005 at 34 medical centers in the United States ($n = 27$), Canada ($n = 6$), and Australia ($n = 1$). Among the 479 participants who were eligible, 375 were enrolled. Data for 4 participants were subsequently excluded because of inadequate consent documentation, withdrawal of consent, or determination of an ineligible diagnosis, leaving a final study population size of 371. The English version of the study materials was administered to 90% of the study population, the French version to 8.4%, and the Spanish version to 1.3%. Characteristics of the 2 treatment groups did not differ significantly at baseline (Table 2).

Attrition and Intervention Adherence

As shown in Fig 1, groups showed similar attrition rates during the 3-month study (17% of intervention group participants and 21% of control participants). Study computers, recovered from all but 1% of participants ($n = 4/371$), indicated an average of 7.7 hours (SE: ±1.0) of use among control group members and 10.7 (±1.0) hours among intervention group members (2-sample t test, $P = .042$). Twenty-two percent of the control group and 33% of the intervention group used their computers for the requested duration of at least 1 hour per week (χ^2 test, $P = .021$). Nine percent of control group participants and 13% of intervention group participants did not play their assigned game(s) at all ($P = .22$), and these individuals were more likely to be nonwhite (15% nonwhite vs 8% white; $P = .049$). African American participants showed the highest nonuse rates (18%, difference from white participants: $P = .051$), and when data were stratified according to condition, African American participants showed increased nonuse rates only in the treatment group ($P = .0086$). African American ethnicity was not associated with nonuse of the game in the control group ($P = .52$). Nonuse rates for Hispanic participants (4%) and participants of mixed or other ethnicity (10%) did not differ significantly from those of white participants (both $P > .58$). In addition, participants who did not play their games at all were more likely to have failed to complete all study visits (ie, skip a study visit or withdraw from the study early; $P = .0009$). This was true in both the treatment and control groups (treatment group $P = .0071$; control group $P = .0066$). African American participants were no more likely to have failed to complete all study visits than other ethnic groups ($P = .66$). Nonuse did not vary as a function of history of video-game play experience before the cancer diagnosis, cancer diagnosis, or sociodemographic factors other than African American ethnicity.

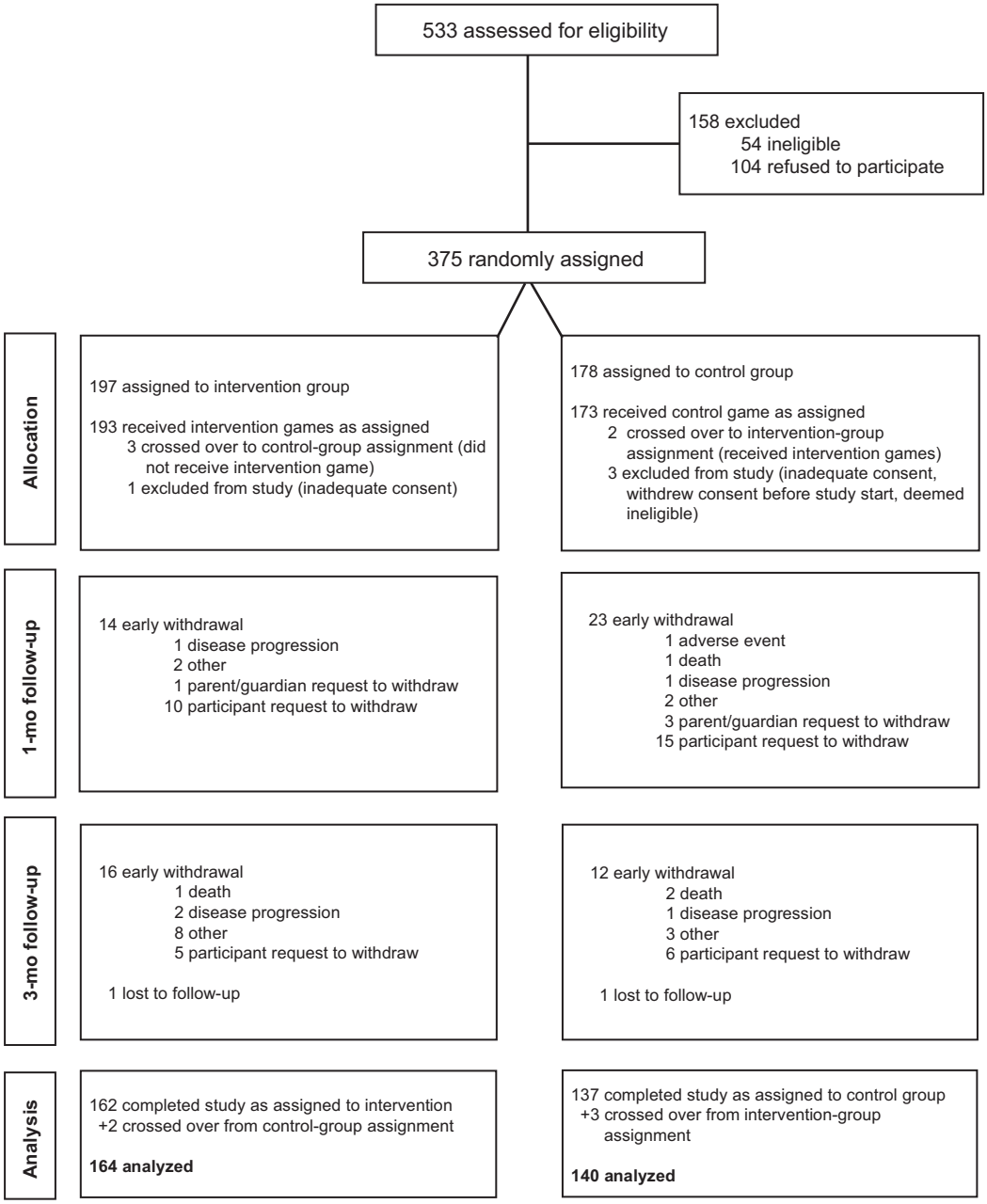

FIGURE 1
Study flow diagram.

Primary Outcomes

Table 3 contains the unadjusted means for each study outcome.

General Treatment Adherence

Self-reported adherence did not differ significantly between groups as measured by the Medication Adherence Scale (group × time interaction, $P = .503$) or the Chronic Disease Compliance Instrument (CDCI) (difference, $P = .78$). Participants in both groups reported uniformly high treatment adherence across assessment time points. Oncology clinic visit attendance was high for both groups (mean: 98 ± 1% of scheduled visits for both intervention and control) and did not differ significantly (Poisson regression for count data, controlling for individual differences in the number of clinic visits scheduled, $P = .65$).

Antibiotic Adherence

Among 200 participants who were prescribed oral TMP/SMX, MEMS-cap monitoring indicated a 16% increase in adherence for intervention group participants (intervention mean: 34.4 ± 2.5 doses; control mean: 29.5 ± 2.6 doses; Poisson regression controlling for individual variation in the prescribed number of doses, $P = .012$; Fig 2A), which corresponds to 62.3% of total prescribed

TABLE 2 **Baseline Participant Characteristics**

Characteristics	Participants, *n* (%)[a]			*P*[b]
	Intervention (*n* = 195)	Control (*n* = 176)	Total Population (*N* = 371)	
Age, y				
13–14	71 (36.4)	60 (34.1)	131 (35.3)	
15–16	56 (28.7)	58 (32.9)	114 (30.7)	.34
17–18	47 (24.1)	32 (18.2)	79 (21.3)	
19–29	21 (10.8)	26 (14.8)	47 (12.7)	
Gender				
Male	132 (67.7)	119 (67.6)	251 (67.7)	.99
Female	63 (32.3)	57 (32.4)	120 (32.3)	
Race/ethnicity				
White	109 (55.9)	101 (57.4)	210 (56.6)	
Hispanic	42 (21.5)	34 (19.3)	76 (20.5)	
Black/African American	19 (9.7)	15 (8.5)	34 (9.2)	
Mixed	9 (4.6)	6 (3.4)	15 (4.0)	
Asian	4 (2.1)	6 (3.4)	10 (2.7)	.40
Native American	2 (1.0)	1 (0.6)	3 (0.8)	
Pacific Islander	0 (0.0)	3 (1.7)	3 (0.8)	
Decline to answer	6 (3.1)	2 (1.1)	8 (2.2)	
Missing	4 (2.1)	8 (4.5)	12 (3.2)	
Education				
Less than high school	76 (39.0)	57 (32.4)	133 (35.8)	
High school	81 (41.5)	77 (43.8)	158 (42.6)	.39
Some college or more	33 (16.9)	33 (18.8)	66 (17.8)	
Not stated	5 (2.6)	9 (5.1)	14 (3.8)	
Annual family income, $[c]				
<10 000	11 (5.6)	17 (9.7)	28 (7.6)	
10 000–19 999	21 (10.8)	18 (10.2)	39 (10.5)	
20 000–39 999	35 (17.9)	24 (13.6)	59 (15.9)	
40 000–59 999	29 (14.9)	20 (11.4)	49 (13.2)	.29
60 000–79 999	15 (7.7)	22 (12.5)	37 (9.9)	
80 000–99 999	16 (8.2)	8 (4.6)	24 (6.5)	
≥100 000	22 (11.3)	18 (10.2)	40 (10.8)	
Declined to answer	46 (23.6)	48 (27.3)	94 (25.3)	
Don't know	0 (0.0)	1 (0.6)	1 (0.3)	
Country of residence				
United States	157 (80.5)	146 (83.0)	303 (81.7)	
Canada	31 (15.9)	27 (15.3)	58 (15.6)	.52
Australia	7 (3.6)	3 (1.7)	10 (2.7)	
Malignancy diagnosis				
Acute lymphoblastic leukemia	76 (38.9)	74 (42.1)	150 (40.4)	
Acute myelogenous leukemia	15 (7.7)	15 (8.5)	30 (8.1)	
Hodgkin's lymphoma	19 (9.7)	16 (9.1)	35 (9.4)	
Non-Hodgkin's lymphoma	17 (8.7)	9 (5.1)	26 (7.0)	.91
Brain tumor	14 (7.2)	14 (7.9)	28 (7.6)	
Osteosarcoma	24 (12.3)	18 (10.2)	42 (11.3)	
Ewing sarcoma	9 (4.6)	10 (5.7)	19 (5.1)	
Other	21 (10.8)	20 (11.4)	41 (11.1)	
Previous disease (relapse/recurrence)				
0	152 (77.9)	136 (77.3)	288 (77.6)	
1	27 (13.9)	30 (17.1)	57 (15.4)	
2	10 (5.1)	8 (4.6)	18 (4.9)	.66
3	4 (2.1)	1 (0.6)	5 (1.4)	
4	2 (1.0)	1 (0.6)	3 (0.8)	
Time since diagnosis for the group without relapse (*n* = 288)				
Median (range), y	0.72 (0.01–15.10)	0.65 (0.01–12.30)	0.69 (0.01–15.14)	
Mean (SD), y	1.53 (2.3)	1.67 (2.5)	1.59 (2.4)	.56
Time since most recent relapse/recurrence (*n* = 83)				
Median (range), y	0.50 (0.01–7.50)	0.45 (0.01–11.80)	0.48 (0.01–11.80)	
Mean (SD), y	0.79 (0.93)	0.84 (1.40)	0.82 (1.20)	.67

TABLE 2 **Continued**

Characteristics	Participants, *n* (%)[a]			*P*[b]
	Intervention (*n* = 195)	Control (*n* = 176)	Total Population (*N* = 371)	
Video-game play history before malignancy diagnosis, h/wk				
No game play	26 (13.3)	22 (12.5)	48 (12.9)	
<1	39 (20.0)	35 (19.9)	74 (20.0)	
1–3	58 (29.7)	49 (27.8)	107 (28.8)	.86
3–8	36 (18.5)	35 (19.9)	71 (19.1)	
≥8	31 (15.9)	26 (14.8)	57 (15.4)	
Missing	5 (2.6)	9 (5.1)	14 (3.8)	

[a] Percentages may not sum to 100% because of rounding.

[b] Test of association from χ^2 test (categorical variables), excluding categories of missing values, or independent *t* test of log-transformed values (continuous variables).

[c] In US dollars.

TMP/SMX doses taken by intervention participants versus 52.5% taken by control participants.

Oral Chemotherapy Adherence

Fifty-four patients were prescribed oral 6-MP as therapy for acute leukemia ($n = 51$) or non-Hodgkin's lymphoma ($n = 3$). Mixed-effect linear model analyses of log-transformed 6MMP concentrations showed that patients in the intervention group maintained significantly higher chemotherapy metabolite levels over time than did patients in the control group (significant group × time interaction; $P = .002$; Fig 2B). Analyses of 6-TG showed a similar pattern but did not reach statistical significance as a result of greater individual variability in blood metabolite levels (Fig 2C). When 6MMP and 6-TG concentrations were analyzed in a single model as distinct indicators of 6-MP metabolism (group × time × metabolite design), a significant group × time interaction also emerged ($P = .041$). Similar results also emerged when data were dichotomized at 6MMP ≤1000 pmol/8 × 10^8 red blood cells (an empirical break point in the 6MMP distribution distinguishing minimal values associated with nonadherence from higher ranging values that likely reflect individual differences in 6-MP metabolism; group × time interaction, $P < .001$). Baseline values of 6MMP or 6-TG did not differ between intervention and control groups (baseline 6MMP $P = .562$; baseline 6-TG $P = .981$).

Self-report Versus Objective Measures of Treatment Adherence

Posthoc correlation analyses (adjusted for multiple comparisons with the Bonferroni correction) were conducted to examine the relationship between self-report measures of adherence (ie, the Medication Adherence Scale and CDCI) and objective measures of adherence (ie, MEMS data and 6-MP metabolite levels). Analyses were conducted on self-report total scores and individual item scores within each measure at each follow-up point and correlated with MEMS percentage of dose taken and 6-MP metabolite levels at each follow-up point. We examined these correlations within study conditions as well. Results revealed no significant relationship between self-report and objective measures of adherence with the exception of 2 items on the CDCI that were related to MEMS assessment of TMP/SMX adherence. On 1 item, patients were asked to rate the extent to which they agreed with the statement, "I feel I am responsible for following my treatment plan as instructed." Patients who agreed with this statement more at the 3-month follow-up than at baseline showed poorer adherence to TMP/SMX (Spearman $r = -0.266$, $P = .0004$). This finding did not hold when each study condition was analyzed separately. For the treatment group, patient agreement with this statement at the 3-month follow-up was associated with greater adherence to TMP/SMX ($r = 0.439$, $P < .0001$) for the duration of the study. Similarly, patients in the treatment group who agreed with the statement, "I have followed the recommended diet," more at the 1-month follow-up compared with baseline showed greater adherence to TMP/SMX ($r = 0.489$, $P = .0006$). No CDCI items were associated with adherence for patients in the control group.

Secondary Outcomes

Cancer-Related Knowledge

Mixed-effect linear model analyses indicated comparable baseline levels of cancer-related knowledge for both groups and a significantly greater increase in cancer-related knowledge over time in the intervention group (group × time interaction, $P = .035$; Fig 3A).

Cancer-Specific Self-efficacy

Mixed-effect linear model analyses indicated similar levels of cancer-specific self-efficacy in intervention and control group participants at baseline but significantly greater increase in self-efficacy over time for members of the intervention group (group × time interaction, $P = .011$; Fig 3B).

Quality of Life, Stress, and Control

Quality of life as assessed by the Pediatric Quality of Life self-report instrument (for participants younger than 18 years) and the Functional Assessment of Cancer Therapy–

TABLE 3 **Observed Means (Raw) of Outcomes at Baseline and Follow-ups According to Study Group**

Outcome Variable	Intervention Group			Control Group		
	Baseline	1 Mo	3 Mo	Baseline	1 Mo	3 Mo
Self-report adherence						
CDCI						
Mean (SD)	79.2 (7.9)	79.0 (8.3)	81.0 (8.7)	77.4 (7.5)	78.4 (7.7)	78.4 (7.5)
n	191	172	163	167	147	140
MAS						
Mean (SD)	2.9 (1.1)	3.0 (1.1)	2.9 (1.1)	2.9 (1.1)	3.1 (1.0)	3.0 (1.1)
n	190	167	160	166	146	138
Adherence to TMP/SMX, % of prescribed doses taken,						
Mean (SD)			62.3 (62.9)			52.5 (37.6)
n			107			93
Adherence to oral 6-MP						
6-TG metabolite assay, mean (SD)	250.7 (245.3)	283.0 (230.1)	286.5 (307.4)	284.3 (206.4)	302.1 (214.0)	236.8 (148.2)
6MMP metabolite assay, mean (SD)	10 484.6 (9920.6)	11 168.9 (12 107.5)	8499.1 (7600.3)	9218.0 (11 004.2)	10 349.9 (11 667.1)	8087.0 (9123.6)
n	28	24	23	26	22	23
Self-efficacy						
Mean (SD)	155.9 (22.3)	158.0 (24.3)	164.1 (23.4)	156.6 (21.3)	157.9 (22.3)	158.8 (23.5)
n	191	172	164	168	148	139
Cancer knowledge						
Mean (SD)	0.59 (0.20)	0.65 (0.20)	0.66 (0.20)	0.60 (0.20)	0.63 (0.20)	0.63 (0.20)
n	191	172	164	168	148	140
Perceived stress						
Mean (SD)	34.4 (7.4)	36.5 (6.6)	38.1 (6.9)	33.1 (6.6)	35.2 (6.8)	35.7 (6.2)
n	191	170	163	168	146	139
Health locus of control						
Internal, mean (SD)	18.9 (6.1)	18.0 (5.9)	17.5 (6.6)	18.6 (5.3)	18.2 (5.8)	17.7 (6.2)
Chance, mean (SD)	20.3 (6.6)	19.1 (6.1)	18.7 (6.8)	20.7 (7.3)	20.0 (6.6)	19.4 (6.9)
Powerful others, mean (SD)	26.4 (4.7)	26.1 (5.1)	25.7 (5.3)	26.5 (4.6)	26.4 (4.6)	26.2 (4.8)
Doctors, mean (SD)	15.2 (2.5)	15.0 (2.8)	14.7 (2.9)	15.4 (2.6)	15.1 (2.8)	15.0 (2.6)
Other people, mean (SD)	11.1 (3.4)	11.2 (3.4)	11.0 (3.7)	11.1 (3.5)	11.4 (3.2)	11.2 (3.3)
n	190	171	164	168	147	139
Quality of life						
PQL (Minor)						
Mean (SD)	64.2 (15.4)	65.5 (15.1)	69.1 (15.1)	62.5 (17.4)	63.5 (17.6)	66.3 (17.3)
n	154	143	119	134	119	102
FACT-G (Adult)						
Mean (SD)	11.3 (2.6)	11.0 (3.2)	12.2 (2.9)	10.7 (2.7)	11.1 (2.1)	11.3 (2.8)
n	32	25	23	31	29	25

[a] 6-TG and 6MMP units of measurement are pmol/8 × 10^8 red blood cells.

General (for participants ≥18 years of age) did not show a significant group × time interaction in primary intention-to-treat analyses (Pediatric Quality of Life, $P = .112$; Functional Assessment of Cancer Therapy–General, $P = .15$). Intervention and control groups also did not differ significantly in the trajectory of scores of self-perceived stress (Perceived Stress Scale) or health locus of control (Multidimensional Health Locus of Control Scale Form) over time (group × time interaction; Perceived Stress Scale, $P = .931$; Multidimensional Health Locus of Control Scale Form, $P = .608$).

Potential Confounders

To determine whether intervention effects varied as a function of gender or ethnicity or country of residence, we analyzed (1) gender × condition × time, (2) ethnicity × condition × time, and (3) country of residence × condition × time interactions. Results generally failed to identify any differential impact as a function of gender, ethnicity, or country of residence. The sole exceptions involved MEMS-cap–measured TMP/SMX use, in which (1) female participants showed a significantly greater positive effect of the intervention than male participants (gender × condition interaction, $P = .028$), and (2) patients in Australia showed the strongest intervention effects, those in the United States showed intermediate effects, and those in Canada showed the weakest effects (country × condition interaction, $P < .0001$). Intervention effects on TMP/SMX use did not differ as a function of race or ethnicity.

Mediation Analyses

Mediation analyses revealed that changes in cancer-related knowledge from baseline to the average value at 1 and 3 months of follow-up did not fully account for the effects of intervention condition on TMP/SMX adherence (intervention effect: $P = .0357$ controlling for cancer knowledge). Similarly, changes in self-efficacy alone

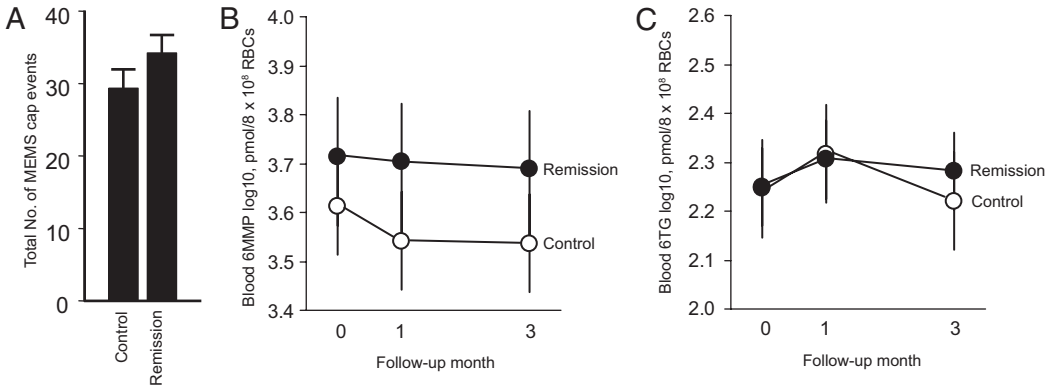

FIGURE 2
Oral medication prescription adherence as measured by frequency (transformed) of TMP/SMX vial cap openings (MEMS) (A) and red cell 6MMP (B) and 6-TG (C) levels according to study group.

did not account for intervention effects on TMP/SMX adherence (intervention effect: $P = .0415$ controlling for self-efficacy in the model); however, analyses that tested self-efficacy and cancer knowledge as joint mediators indicated that these factors together were sufficient to account for all significant effects of intervention condition on TMP/SMX adherence (residual intervention effect $P = .2384$, controlling for both self-efficacy and knowledge). Parallel mediation analyses on 6-MP adherence involving self-efficacy, knowledge, or both variables simultaneously did not account for intervention effects (ie, after controlling for change over time in those variables, intervention condition patients continued to show significantly more favorable trends over time in 6MMP metabolite levels alone, the sum of 6MMP and 6-TG levels, and a repeated-measures analysis that considered 6MMP and 6-TG as separate indicators).

Intervention Adherence Analyses

Given that only 28% of participants fully adhered to the requested 1 hour of game play per week, we sought to determine whether game-play adherence influenced the magnitude of intervention effects on medication adherence. Analysis of MEMS-cap data and 6-MP chemotherapy metabolite levels found similarly strong intervention effects for both those who played less than the requested 12 hours during the 3-month study duration and those who played more (ie, computer adherence × group interaction for TMP/SMX, $P = .12$; and computer adherence × group × time interaction term for simultaneous analysis of 6MMP and 6-TG levels, $P = .62$). Similar findings emerged when analyses distinguished between those who played their assigned game <50% of the requested amount (ie, <6 hours during the course of the entire study). Results continued to indicate a significant beneficial effect of the intervention despite suboptimal game use (6-MP metabolites: group × time interaction, $P = .024$; TMP/SMX use: group effect, $P = .005$).

Adverse Events

One study participant reported a trial-related adverse event. A member of the control group complained of dizziness only while playing the control game. No physiologic causes were found for the dizziness (eg, fluid behind the ears). The patient was withdrawn from the study.

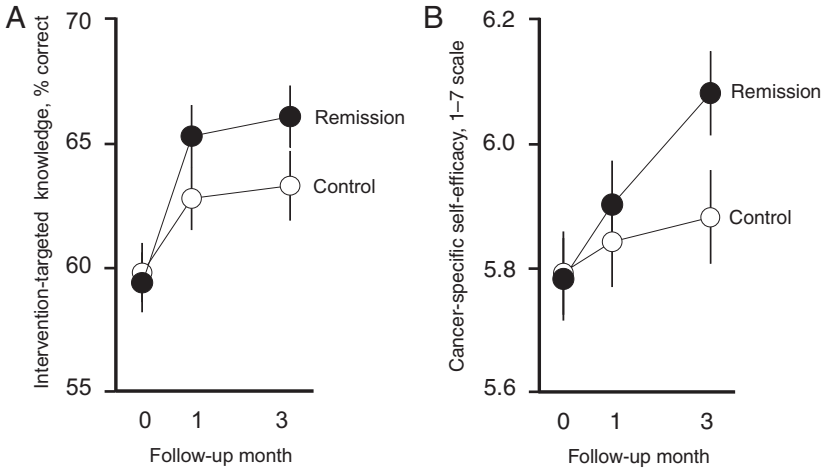

FIGURE 3
Mean (transformed) cancer-related knowledge (A) and self-efficacy scores (B) at baseline and follow-ups according to study group.

DISCUSSION

Results from this multicenter, randomized trial suggest that a behaviorally targeted video-game intervention can enhance adherence to prescribed oral medication regimens in AYA with cancer. These improvements in adherence to therapy are clinically relevant because patients who have cancer and are adherent to oral antibiotic prophylactic regimens have a lower incidence of fevers and infections[13,72] and increased survival,[5] and those who adhere to oral 6-MP chemotherapy regimens show improved survival outcomes.[12,16] The results from this study also showed increases in self-efficacy and cancer-related knowledge among patients who were randomly assigned to the intervention, and these changes may contribute to the intervention's effects on the primary end point of adherence. Self-efficacy and knowledge together were also shown to mediate improvements that were observed in patient adherence to TMP/SMX (although not to 6-MP). Taken together, the findings in this study indicate that an easily distributed video-game–based intervention can have a positive impact on treatment-relevant behaviors and outcomes in a patient population with a serious life-threatening illness.

The interactive game-based intervention that was evaluated in this study represents a novel approach for optimizing patient behavioral participation in cancer treatment regimens. Additional research is needed to define the specific psychological mechanisms by which this game-based approach affects health behaviors; however, consistent with social learning theory,[62] these results suggest that changes in cancer-specific self-efficacy and knowledge about cancer contribute to treatment adherence, specifically to the oral antibiotic TMP/SMX. Several other psychological factors were not significantly altered by this intervention (eg, stress, quality of life, perceived control over health). This pattern of results is consistent with previous studies that highlighted self-efficacy as particularly sensitive to video-game–based intervention.[27] Additional research will also be required to evaluate the scope of behavioral processes that are amenable to change through game-based interventions. This research should also investigate why self-efficacy and knowledge mediated adherence to TMP/SMX but not to oral 6-MP chemotherapy, with a focus on determining whether factors that were not measured in this study, such as anxiety, might have mediated intervention effects on this outcome. Also, the impact of improved adherence to prophylactic antibiotics in the intervention group (approximately one third of doses missed versus one half in the control group) should be investigated further to clarify how much this statistical improvement improves morbidity outcomes and survival rates in this population.

This intervention specifically targeted self-administered oral medication adherence as a component of game play. Self-administered antibiotics and chemotherapy may be particularly amenable to patient-targeted behavioral intervention, and it is unclear whether game-based approaches might affect other behavioral components of cancer treatment. For example, self-report measures of general treatment adherence and clinician-reported attendance at scheduled outpatient clinic visits were not significantly enhanced by this intervention; however, both of those measures were very high at baseline, suggesting that there was little room for improvement. Finally, the absolute lack of adverse effects that were associated with playing the intervention game suggests that it is safe for dissemination to a patient population.

Strengths of this study include the use of a randomized, controlled trial design; a relatively large sample size; a multimodal approach to assessing outcomes (self-report and objective measures); and broad representation of ethnic minority groups in the study population. Limitations include the heterogeneity of cancer diagnoses and treatment regimens and the nonuniform trial entry at varying treatment stages. Although this heterogeneity may reduce statistical power, it may improve generalizability of the findings for application in a broad array of AYA patients with cancer. Direct measures of adherence to TMP/SMX and oral 6-MP were obtained from the subset of the sample who were prescribed these medications, thus making it impossible to determine whether patients who are prescribed other medications would show similar patterns of adherence to their medications if exposed to the intervention game. Male patients were overrepresented among study participants, perhaps because of greater appeal of video games to that audience; however, intervention effects were similar for both genders but with a somewhat greater impact on oral TMP/SMX adherence for female patients. A final limitation involves suboptimal adherence to the video-game intervention, which was used less than the requested amount by most participants in this study. Despite this, there were significant positive effects of Re-Mission even for participants who played the game $<50\%$ of the requested duration. This suggests that shorter durations of play could be recommended during dissemination of the game, which could make this intervention more appealing to patients with a high treatment burden. Some groups demonstrated particularly low game-play rates (eg, African American patients), suggesting that targeted improvements may need to be made to increase the appeal of the game in certain subgroups. Finally, generalizability of the findings may be somewhat limited because access to personal computers that are needed to play the game(s) were provided as part of the study and may not reflect patient access to similar technology in the "real world." Thus, implementation of this intervention should include efforts to ensure that the necessary computer resources are available.

CONCLUSIONS

This study provides preliminary empirical support for the efficacy of a video-game intervention in improving behavioral outcomes in AYA with cancer. Given the role of behavioral factors in influencing chronic disease management more broadly, similar approaches could potentially be directed toward a variety of chronic diseases as an easily distributable approach to improving behavioral disease management. As such, video-game–based inter-

ventions may constitute one component of a broader integrative approach to health care that synergistically combines rationally targeted biological and behavioral interventions to aid patients in the prevention, detection, treatment, and recovery from disease. More broadly, the current results suggest that a carefully designed video game can have a positive impact on health behavior in young people with chronic illness.

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Dr Kato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Drs Kato, Cole, Pollock, and Bradlyn were involved in study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and administrative, technical, or material support; Dr Kato was responsible for acquisition of data and obtaining funding; Drs Cole and Pollock were responsible for statistical analysis; and Drs Kato and Pollock were responsible for study supervision.

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