Universiteit Leiden
The Netherlands

Unraveling dexamethasone-induced neurobehavioral and sleep problems in children with ALL: which determinants are important?

Hulst, A.M. van; Grootenhuis, M.A.; Verwaaijen, E.J.; Litsenburg, R.R.L., van; Li, L.; Zelst, B.D. van; ... ; Heuvel-Eibrink, M.M. van den

Citation
Hulst, A. M. van, Grootenhuis, M. A., Verwaaijen, E. J., Litsenburg, R. R. L. , van, Li, L., Zelst, B. D. van, ... Heuvel-Eibrink, M. M. van den. (2023). Unraveling dexamethasone-induced neurobehavioral and sleep problems in children with ALL: which determinants are important? *Jco Precision Oncology*, *7*. doi:10.1200/PO.22.00678

Version:	Publisher's Version
License:	Creative Commons CC BY-NC-ND 4.0 license
Downloaded from:	https://hdl.handle.net/1887/4247171

Note: To cite this publication please use the final published version (if applicable).

Check for updates

Unraveling Dexamethasone-Induced Neurobehavioral and Sleep Problems in Children With ALL: Which Determinants Are Important?

Annelienke M. van Hulst, MD[1]; Martha A. Grootenhuis, Prof Dr[1]; Emma J. Verwaaijen, MSc[1]; Raphaële R.L. van Litsenburg, MD, PhD[1]; Letao Li, MSc[2]; Bertrand D. van Zelst, BSc[3]; Linda Broer, PhD[4]; Saskia M.F. Pluijm, PhD[1]; Rob Pieters, MD[1]; Marta Fiocco, Prof Dr[1,5,6]; Erica L.T. van den Akker, MD[7]; and Marry M. van den Heuvel-Eibrink, MD[1,8]

DOI https://doi.org/10.1200/PO.22.00678

ABSTRACT

PURPOSE Dexamethasone, the preferred corticosteroid in most treatment protocols for pediatric acute lymphoblastic leukemia (ALL), can induce undesirable side effects. Neurobehavioral and sleep problems are frequently reported, but the interpatient variability is high. We therefore aimed to identify determinants for parent-reported dexamethasone-induced neurobehavioral and sleep problems in pediatric ALL.

METHODS Our prospective study included patients with medium-risk ALL and their parents during maintenance treatment. Patients were assessed before and after one 5-day dexamethasone course. Primary end points were parent-reported dexamethasone-induced neurobehavioral and sleep problems, measured with the Strengths and Difficulties Questionnaire and Sleep Disturbance Scale for Children, respectively. Analyzed determinants included patient and parent demographics, disease and treatment characteristics, parenting stress (Parenting Stress Index and Distress Thermometer for Parents), dexamethasone pharmacokinetics, and genetic variation (candidate single-nucleotide polymorphisms *rs41423247* and *rs4918*). Statistically significant determinants identified in univariable logistic regression analyses were incorporated in a multivariable model.

RESULTS We included 105 patients: median age was 5.4 years (range, 3.0-18.8) and 61% were boys. Clinically relevant dexamethasone-induced neurobehavioral and sleep problems were reported by parents in 70 (67%) and 61 (59%) patients, respectively. In our multivariable regression models, we identified parenting stress as a significant determinant for parent-reported neurobehavioral (odds ratio [OR], 1.16; 95% CI, 1.07 to 1.26) and sleep problems (OR, 1.06; 95% CI, 1.02 to 1.10). Furthermore, parents who experienced more stress before start of a dexamethasone course reported more sleep problems in their child (OR, 1.16; 95% CI, 1.02 to 1.32).

CONCLUSION We identified parenting stress, and not dexamethasone pharmacokinetics, genetic variation, patient/parent demographics, or disease/treatment characteristics, as a significant determinant for parent-reported dexamethasone-induced neurobehavioral and sleep problems. Parenting stress may be a modifiable target to reduce these problems.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Accepted April 24, 2023
Published June 21, 2023

JCO Precis Oncol 7:e2200678

© 2023 by American Society of Clinical Oncology

Creative Commons Attribution Non-Commercial No Derivatives 4.0 License

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.

INTRODUCTION

Dexamethasone is currently the preferred corticosteroid in most treatment protocols for pediatric acute lymphoblastic leukemia (ALL).[1-3] However, dexamethasone has various undesirable side effects. Patients and parents often report neurobehavioral problems as harmful side effects, which generally negatively affect quality of life.[4-6] These neurobehavioral problems include mood swings and behavioral changes but also depression or psychosis, and occur in 5%-75% of patients.[7-10] Sleep problems, such as insomnia and hypersomnia, are also well-established adverse effects of supraphysiologic steroid treatment in children, with an estimated prevalence between 19% and 87%.[11-14]

For better understanding of the differences between patients and parents who do and do not report dexamethasone-induced neurobehavioral or sleep problems and to develop targeted interventions, it is important to identify contributing determinants. Our recent systematic review

CONTEXT

Key Objective

Patient, parent, or treatment characteristics, parenting stress, genetic susceptibility, or dexamethasone kinetics: which determinants may explain the variability in dexamethasone-induced neurobehavioral and sleep problems in children with acute lymphoblastic leukemia (ALL)?

Knowledge Generated

Parenting stress was identified as significant determinant for both parent-reported dexamethasone-induced neurobehavioral and sleep problems. We did not establish an association between dexamethasone pharmacokinetics, genetic variation, patient or parent demographics, or disease and treatment characteristics, and behavioral or sleep problems.

Relevance

Neurobehavioral and sleep problems, which are reported by parents in the majority of patients, are burdensome side effects of dexamethasone treatment. Targeting parenting stress may be a useful intervention to decrease neurobehavioral and sleep problems in children with ALL.

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.

recognized younger patient age as a potential determinant for dexamethasone-induced neurobehavioral problems, whereas older patients are at risk of sleep problems.[15] Furthermore, single-nucleotide polymorphisms (SNPs) may contribute to interindividual differences.[16] Two small studies suggested an association between the *Bcl-1* polymorphism (*glucocorticoid receptor* [*GR*] gene) and depressive symptoms.[17,18] The *rs4918* polymorphism (*alpha2-HS glycoprotein* [*AHSG*] gene) was suggested to be associated with impaired sleep during dexamethasone treatment in patients with ALL.[19] However, these results remain to be replicated. Furthermore, in adults, a higher steroid dose appears to increase the risk of steroid-induced mental disorders.[20] Younger children have a higher dexamethasone clearance[21]; however, the role of dexamethasone pharmacokinetics in the occurrence of neurobehavioral or sleep problems remains unclear. Other possible determinants such as parenting stress, parental coping, or (medical) background have only been suggested in case reports and series.[15] Besides, a large drawback of most studies that investigated prognostic factors for dexamethasone-induced side effects are their retrospective nature and/or use of unvalidated outcome measurement tools.

Therefore, our current study aimed to identify possible determinants for dexamethasone-induced parent-reported neurobehavioral and sleep problems, in a prospective national cohort of pediatric patients with ALL, using validated questionnaires. In addition, we explored parental coping during dexamethasone treatment, since this may be an important and modifiable factor for possible interventions.

METHODS

Study Design and Participants

This prospective study was pursued in the setting of a randomized controlled trial, of which the design was previously reported.[22] Additional relevant methods are available as Data Supplement. In brief, patients age between 3 and 18 years, treated according to the Dutch Childhood Oncology Group ALL-11 protocol who received dexamethasone during medium-risk group maintenance treatment and their parents were asked to participate.

All included patients were assessed on the first day (T1), before the start of a dexamethasone course, and after 5 full days (T2) of dexamethasone (6 mg/m²/d). Peripheral blood samples were obtained on both days. Parents were asked to complete questionnaires on both days (Fig 1). All parents and/or patients provided written informed consent to participate. The study was approved by the Medical Ethical Committee of Rotterdam (NL62388.078.17).

Outcome Measures

Neurobehavioral Problems

We used the validated Dutch version of the parent-reported Strengths and Difficulties Questionnaire (SDQ) to assess neurobehavioral problems.[23-27] This questionnaire measures psychological adjustment of children and adolescents using five subscales: emotional symptoms, conduct problems, hyperactivity-inattention, peer problems, and prosocial behavior. The total difficulties score was calculated by adding the first four subscales; a higher score reflects more problems. Outcome measures were dichotomized: an increase of ≥5 points after 5 days of dexamethasone was considered as clinically relevant dexamethasone-induced neurobehavioral problems.[11] The SDQ is also available as self-report for children age 11 years and older and was therefore offered to these patients.[27]

Sleep Problems

Sleep quality was assessed with the parent-reported Sleep Disturbance Scale for Children (SDSC).[28,29] This validated

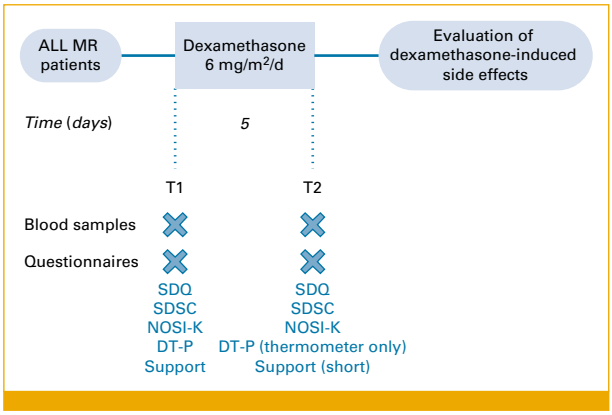

FIG 1. Study design. Patients with ALL were included during maintenance therapy. Before (T1) and after (T2) 5 days of dexamethasone treatment, peripheral blood samples were collected and validated questionnaires were filled in by parents. At T2, the DT-P consisted of only the thermometer, and the support questionnaire was one additional question. ALL, acute lymphoblastic leukemia; DT-P, Distress Thermometer for Parents; MR, medium risk; NOSI-K, Nijmeegse Ouderlijke Stress Index Korte versie (shortened Dutch version of the Parenting Stress Index); SDQ, Strengths and Difficulties Questionnaire; SDSC, Sleep Disturbance Scale for Children.

questionnaire yields six subscales: disorders of initiating and maintaining sleep (DIMS), sleep breathing disorders (SBD), disorders of arousal (DA), sleep-wake transition disorders (SWTD), disorders of excessive somnolence (DES), and sleep hyperhidrosis (SHY). The sum provides a total sleep score; a higher score reflects more problems. An increase of ≥7 points on this total score, after 5 days of dexamethasone, was considered as clinically relevant sleep problems.[11] The SDSC is not available as self-report.

Determinants

Patient and Parent Demographics, Disease, and Treatment Characteristics

Patient, treatment, and disease characteristics taken into account were age, sex, week in maintenance phase, ALL subtype (B-cell ALL or T-cell ALL), concurrent asparaginase use,[21] and CNS involvement. Both the SDQ total difficulties and the SDSC total score at T1 (ie, pre-existing neurobehavioral or sleep problems) were evaluated as possible determinants. Family characteristics taken into account were number of siblings and parental factors such as age, nationality, highest level of education of both parents, and which parent completed the questionnaires.

Support and Parental Coping

We developed a short survey regarding received support (see Data Supplement). Questions concerned whether a child and/or parent received psychological or other support and why. Furthermore, since it is known from literature that coping with dexamethasone pulses in maintenance treatment can be extremely stressful,[4] we asked parents to qualitatively describe how they cope with the dexamethasone treatment: how do they prepare their family and how do they manage during the treatment days. The qualitative responses were collected and predefined keywords were highlighted (eg, nothing/normal or resting). If a response which was not predefined was noted more than five times, this was also highlighted (eg, lax parenting). The highlighted keywords were totaled.

At T2, one question regarding received support during the dexamethasone course was included.

Parenting Stress

To measure parenting stress at T1 and T2, we used the Nijmeegse Ouderlijke Stress Index Korte versie (NOSI-K),[30] an adapted version of the Parenting Stress Index.[31] This validated 25-item questionnaire measures stress experienced within the parenting role. A higher score reflects higher stress levels (range, 25-150).

We also used the Distress Thermometer for Parents (DT-P).[32] This validated questionnaire consists of three parts: (1) a thermometer (visual analog scale) ranging from 0 (no distress) to 10 (extreme distress), (2) a total score on the basis of a problem list about everyday problems, and (3) additional questions concerning support, lack of understanding, and parental chronic illness. The total questionnaire and thermometer were completed by parents at T1, and the thermometer at T2.

Dexamethasone Pharmacokinetics

At T1, a peripheral blood sample was obtained approximately 2 hours after the first dexamethasone dose on day 1 (peak level). The exact time of intake and blood sampling was registered. For the measurement at T2 (trough level), parents were asked to document the exact time of the last dexamethasone administration the evening before. The moment of T2 blood sampling was registered. To calculate AUC of dexamethasone, we selected patients with both a peak and trough measurement concentration value within 24 hours after dexamethasone administration. We calculated slope and intercept values of the concentration and time after dose (0-24 hours) plots for each patient using a linear regression method. We then used these values to get the extrapolated intercept on both x-axis and y-axis and calculated the triangle area as the AUC in each patient (Eq 1).

$$AUC = \frac{intercept_x * \text{intercept}_y}{2} \quad (1)$$

Candidate SNP Assessment

We used a candidate SNP approach, analyzing whether *Bcl1* (*rs41423247 G>C, GR* gene) and *rs4918 C>G* (*AHSG* gene) polymorphisms were associated with dexamethasone-induced neurobehavioral or sleep problems, respectively.[17-19] We

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.

analyzed both dominant models (eg, CC *v* CG + GG: heterozygous carrier status) and recessive models (eg, CC + CG *v* GG: homozygous carrier status). Details about the methodology are available in the Data Supplement documents.

Statistical Analyses

Descriptive statistics with either means and standard deviations or medians with IQRs were calculated. The difference between SDQ and SDSC scores at T1 versus T2 was tested with a Wilcoxon signed-rank test. The intraclass correlation coefficient (ICC) was calculated to compare SDQ data of parents and children (two-way mixed-effects model, single measures, absolute agreement).

Univariable logistic regression models were estimated to explore associations between the potential determinants and either neurobehavioral or sleep problems. Odds ratios (ORs) with 95% CIs were estimated. Significant determinants with a *P* value <.20 and four or more patients in each cell of the contingency table were included in the multivariable model. Furthermore, variables that were clinically relevant on the basis of reported literature (patient age and sex[15,33,34] and maintenance week[35,36]), as well as T1 SDQ score (for neurobehavioral problems) and T1 SDSC score (for sleep problems), were included in the multivariable logistic regression model. Multicollinearity was checked as described before.[37] All analyses were performed using IBM SPSS Statistics version 26.0.

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.

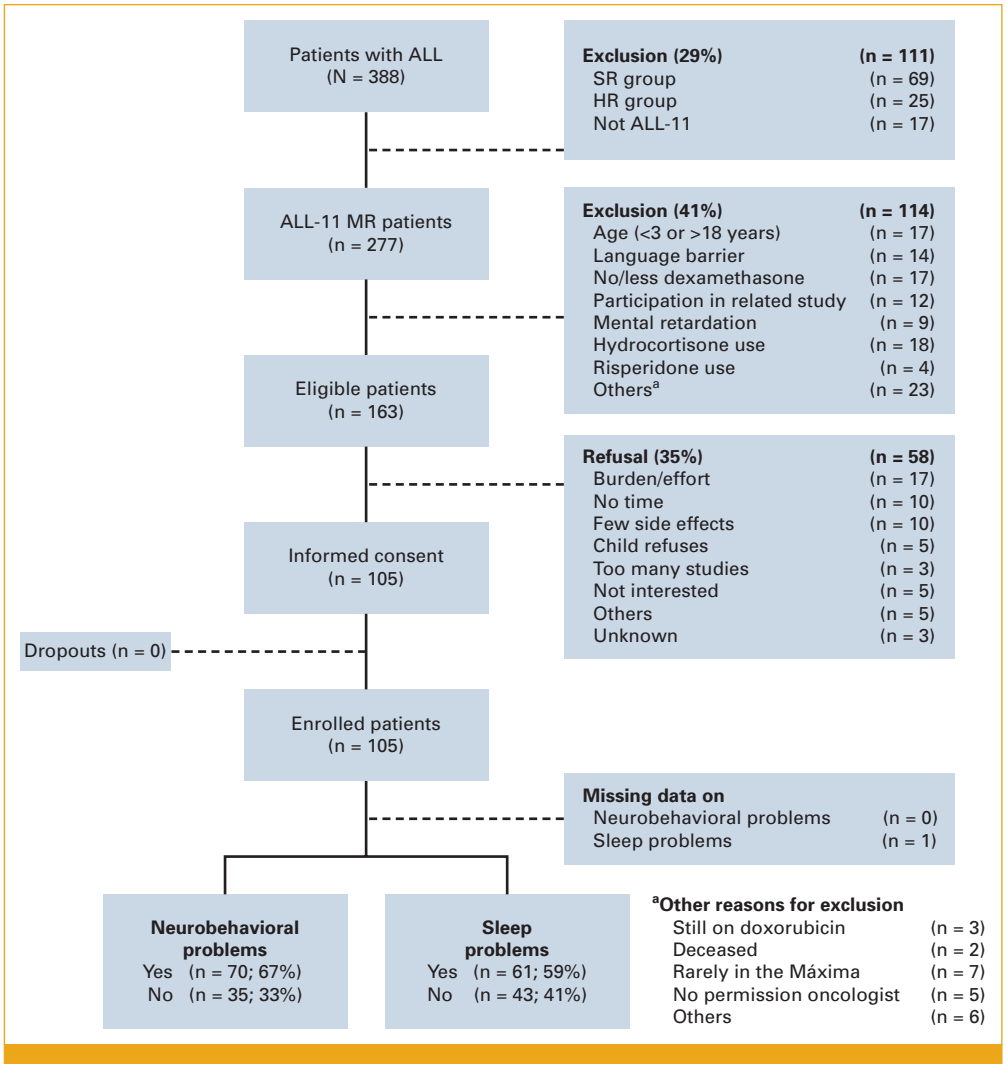

FIG 2. Flow diagram. Eligible patients with ALL were approached for inclusion after approval of the treating pediatric oncologist. Reasons for refusal were stated by parents or patients. Patients with a rise of five points on the SDQ or seven points on the SDSC after 5 days of dexamethasone treatment were classified as having clinically relevant dexamethasone-induced neurobehavioral or sleep problems, respectively. ALL, acute lymphoblastic leukemia; HR, high risk; MR, medium risk; SDQ, Strengths and Difficulties Questionnaire; SDSC, Sleep Disturbance Scale for Children; SR, standard risk.

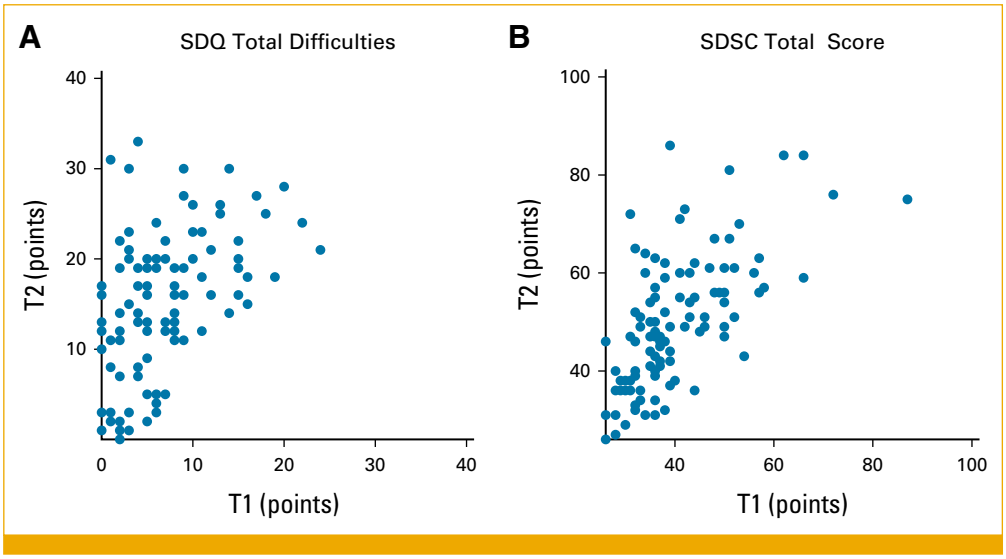

FIG 3. (A) SDQ and (B) SDSC scores before (T1) and after (T2) a 5-day dexamethasone course. Each dot depicts one patient. Overall, the SDQ and SDSC scores rise between T1 and T2. SDQ, Strengths and Difficulties Questionnaire; SDSC, Sleep Disturbance Scale for Children.

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.

RESULTS

In this nationwide study, patients and their parents were recruited in the Princess Máxima Center for pediatric oncology in the Netherlands between May 17, 2018, and March 27, 2021. Of 163 eligible patients, 105 were included in our study (Fig 2). Nonresponders did not differ significantly on baseline characteristics compared with included patients. The median age of the included patients was 5.4 years (range, 3.0-18.8) and 61% were boys. All parents completed the SDQ at T1 and T2; the SDSC was missing in one case. The SDQ increased from median 5 points (IQR, 3-10) to 16 points (IQR, 11-20; $P < .001$). The SDSC score increased from median 37 points (IQR, 32-46) to 48 points (IQR, 38-59; $P < .001$; Fig 3). Clinically relevant dexamethasone-induced neurobehavioral or sleep problems were reported by parents in 70 (67%) and 61 (59%) of the patients, respectively. In 53 patients (50%), both problems were reported, whereas in 27 patients (26%), no clinically significant problems occurred (Fig 4). Baseline characteristics did not differ between groups (Table 1).

The results from all questionnaires were low to moderately correlated with each other at T1 (Pearson correlation 0.3-0.7; Data Supplement [Supplemental Table 1]).

Of the 105 included patients, 19 (18.1%) were age 11 years or older and therefore offered the SDQ self-report. Twelve patients (63%) completed the SDQ at both time points, four patients (21%) at one time point, and three patients (16%) did not complete any SDQ. The T1 ICC was 0.40 (95% CI, −0.11 to 0.72). For T2, the ICC was 0.73 (95% CI, 0.34 to 0.91). The ICC of the delta SDQ score was 0.30 (95% CI, −0.24 to 0.72).

Dexamethasone-Induced Neurobehavioral Problems

In univariable regression analyses, child age, SDQ T1 score, maternal age and nationality, paternal age and nationality, and NOSI-K and DT-P delta and T2 scores (reflecting parenting stress during a dexamethasone course of the child) were associated with parent-reported clinically relevant dexamethasone-induced neurobehavioral problems (Data Supplement [Supplemental Table 2]).

Dexamethasone levels (AUC estimated values) were assessed in 86 patients. We did not find an association between dexamethasone AUC and neurobehavioral problems, even

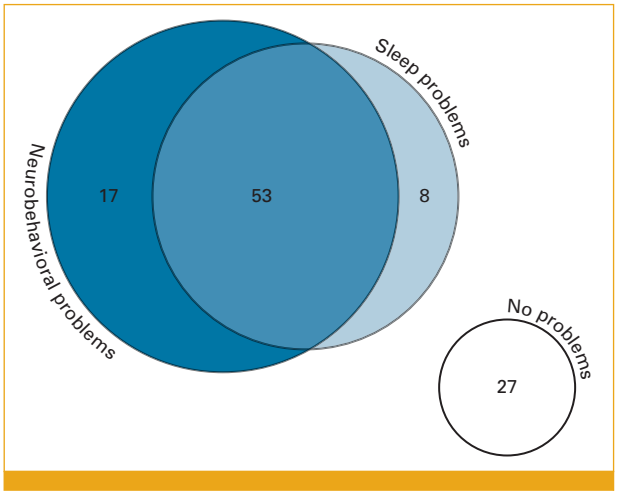

FIG 4. Venn diagram of dexamethasone-induced neurobehavioral and sleep problems. Neurobehavioral problems were reported in 70 patients and sleep problems in 61 patients. In 27 patients, no clinically relevant problems were reported.

TABLE 1. Baseline Characteristics

Characteristic	Total Group (n = 105)	Outcomes				
		Neurobehavioral Problems		Sleep Problems		No Clinically Significant Problems (n = 27)
		No (n = 35)	Yes (n = 70)	No (n = 43)	Yes (n = 61)	
Age, years, median (IQR)	5.4 (4.1-8.9)	5.8 (4.3-13.1)	5.3 (4.0-8.4)	5.5 (4.0-9.8)	5.3 (4.1-8.4)	5.4 (4.0-12.1)
Sex, No. (%)						
Boy	64 (61)	23 (65.7)	41 (58.6)	28 (65.1)	35 (57.4)	17 (63)
Girl	41 (39)	12 (34.3)	29 (41.4)	15 (34.9)	26 (42.6)	10 (37)
Week maintenance, median (IQR)	34 (22-43)	37 (27-43)	33 (21-44)	33 (22-43)	37 (28-48)	34 (25-43)
Asparaginase during study, No. (%)						
No	93 (88.6)	32 (91.4)	61 (87.1)	37 (86.0)	56 (91.8)	25 (92.6)
Yes	12 (11.4)	3 (8.6)	9 (12.9)	6 (14.0)	5 (8.2)	2 (7.4)
Type ALL,[a] No. (%)						
B-cell ALL	93 (88.6)	30 (85.7)	63 (90)	39 (90.7)	53 (86.9)	24 (88.9)
T-cell ALL	11 (10.5)	4 (11.4)	7 (10)	3 (7.0)	8 (13.1)	2 (7.4)
CNS involvement,[b] No. (%)						
No	85 (81)	27 (77.1)	58 (82.9)	35 (81.4)	49 (80.3)	20 (74.1)
Yes	20 (19)	8 (22.9)	12 (17.1)	8 (18.6)	12 (19.7)	7 (25.9)

Abbreviations: BPDCN, blastic plasmacytoid dendritic cell neoplasm; MRG, medium-risk group; TLP, traumatic lumbar puncture.
[a]One patient with BPDCN.
[b]Patients with CNS involvement (defined as CNS-3 or other CNS manifestations at diagnosis, or TLP+) receive two additional intrathecal therapy administrations and are considered as CNS involvement yes. MRG patients without CNS involvement receive 13 intrathecal administrations, and with CNS involvement 15.

after adjusting for concomitant asparaginase use, which may influence dexamethasone pharmacokinetics.[21]

Genetic susceptibility data were available for all 105 patients. Neither homozygous nor heterozygous carrier status of the *Bcl-1* polymorphism was associated with neurobehavioral problems in our cohort (Data Supplement [Supplemental Table 2]).

The multivariable model (Table 2) included patient age and sex, maintenance week, SDQ T1 score, maternal age and nationality, and parenting stress (NOSI-K delta score). In multivariable analysis, parenting stress (OR, 1.16; 95% CI, 1.07 to 1.26) remained statistically significantly associated with parent-reported neurobehavioral problems. A one-point increase on the NOSI-K delta score (range, −125 to 125) led to 16% higher odds of parent-reported

TABLE 2. Multivariable Regression Models

Determinant	Neurobehavioral Problems		Sleep Problems	
	OR	95% CI	OR	95% CI
Age, years	1.00	0.80 to 1.26	1.07	0.93 to 1.24
Sex	1.26	0.32 to 5.04	0.89	0.28 to 2.66
Week maintenance	0.99	0.94 to 1.04	1.02	0.98 to 1.06
SDQ/SDSC score T1[a]	**0.82**	**0.68 to 0.99**	**0.93**	**0.87 to 1.00**
Parenting stress during dexamethasone[b]	**1.16**	**1.07 to 1.26**	**1.06**	**1.02 to 1.10**
Nationality mother	0.62	0.05 to 7.25	0.54	0.10 to 3.03
Age mother, years	0.90	0.78 to 1.04	—	—
Parental stress T1[c]	—	—	**1.16**	**1.02 to 1.32**
Psychological support child	—	—	0.24	0.05 to 1.26

NOTE. Values in bold are statistically significant ($P < .05$).
Abbreviations: DT-P, Distress Thermometer for Parents; NOSI-K, Nijmeegse Ouderlijke Stress Index Korte versie (shortened Dutch version of the Parenting Stress Index); OR, odds ratio; SDSC, Sleep Disturbance Scale for Children; SDQ, Strengths and Difficulties Questionnaire.
[a]T1 SDQ and SDSC scores were included for neurobehavioral and sleep problems, respectively.
[b]Parenting stress during dexamethasone is indicated by the NOSI-K delta score (corrected for the T1 NOSI-K score).
[c]Parental stress is indicated by the DT-P total score measured at T1.

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.

dexamethasone-induced neurobehavioral problems, corrected for the other included variables. SDQ T1 score also remained statistically significant (OR, 0.82; 95% CI, 0.68 to 0.99), indicating that parents of children who had a higher SDQ score at T1 reported less dexamethasone-induced neurobehavioral problems.

Dexamethasone-Induced Sleep Problems

The following determinants had a *P* value <.20 in univariable regression analyses for sleep problems: SDSC T1 score, maternal nationality, NOSI-K delta score and DT-P thermometer T2 score (reflecting parenting stress during dexamethasone treatment of the child), DT-P total score (reflecting parental stress before the start of a dexamethasone course), and psychological support of the child (Data Supplement [Supplemental Table 3]). No significant association was found between other determinants, such as dexamethasone pharmacokinetics or carrier status of *rs4918*, and dexamethasone-induced sleep problems in our cohort (Data Supplement [Supplemental Table 3]).

The multivariable logistic regression model included age and sex of the child, maintenance week, SDSC T1 score, maternal nationality, parenting stress (delta NOSI-K), and parental stress (DT-P total score; Table 2). Parenting stress during dexamethasone (delta NOSI-K) remained statistically significantly associated with parent-reported sleep problems of the children (OR, 1.06; 95% CI, 1.02 to 1.10). A one-point rise on the NOSI-K delta score led to 6% higher odds of parent-reported dexamethasone-induced sleep problems, corrected for the other included variables. Furthermore, both SDSC T1 score (OR, 0.93; 95% CI, 0.87 to 1.00) and parental stress at T1 (DT-P total score, OR, 1.16; 95% CI, 1.02 to 1.32) were significantly associated with sleep problems, indicating that parents of children who had a higher SDSC score at T1 reported less dexamethasone-induced sleep problems, whereas parents who experienced more stress before the start of a dexamethasone course reported more sleep problems in their child.

Parental Experiences and Coping

Ninety-eight parents (93%; 79 mothers and 19 fathers) completed two questions concerning their experiences with dexamethasone and parental coping; multiple responses were possible. Parents' ways of managing during the dexamethasone courses differed from doing nothing extra or acting normal to merely surviving. Phrases like "it is doom and gloom" and "these 5 days are exhausting" were mentioned by parents. Interestingly, 26 parents spontaneously indicated that they wield lax(er) parenting strategies during dexamethasone treatment.

DISCUSSION

Our prospective national cohort study in 105 pediatric patients with ALL identified parenting stress as a significant determinant for both parent-reported dexamethasone-induced neurobehavioral and sleep problems. We did not find an association between dexamethasone pharmacokinetics, genetic variation, patient and parent demographics, or disease and treatment characteristics, and behavioral or sleep problems.

Parents with higher levels of parenting stress during a dexamethasone course of their child reported more dexamethasone-induced neurobehavioral and sleep problems in their children. In addition, parents with more stress before the start of a dexamethasone course reported more sleep problems. The direction of these associations, however, is unclear: parenting stress may lead to disruptive child behavior and perceived sleep problems, vice versa, or the association may be bidirectional. To strengthen our finding, the association between parenting stress and child problems during dexamethasone should be established in an independent cohort. Moderating factors such as other stressful life events could play a role in both parenting stress and child behavioral problems.[38] Previous studies showed that children of parents with higher levels of parenting stress showed more behavioral adjustment problems after ALL diagnosis.[39,40] Also, parental distress and child distress are more strongly linked in a pediatric cancer cohort compared with controls.[38] Targeting parenting stress, in individual cases, may be a useful intervention to decrease behavioral and sleep problems in children. Fedele et al[41] showed that a randomly allocated psychosocial intervention focusing on uncertainty, coping, communication, support, and problem solving for mothers reduced internalizing symptoms in children with cancer. Similarly, Williams et al[42] pursued a successful evidence-based parenting intervention for parents with a child in ALL maintenance treatment. Although this study involved only 12 patients, it showed both an improvement in quantitative difficulties (SDQ) and qualitative behavioral improvement (indicated by parents).

Parents of children with a higher SDQ or SDSC score at T1 reported less dexamethasone-induced neurobehavioral and sleep problems, respectively. This could indicate that, when parents already notice more problems in their child, the change during dexamethasone may be less pronounced. Also, if a child has a higher score at T1, a rise of 5 (SDQ) or 7 (SDSC) points may be more difficult to achieve. Still, pre-existing problems and parents' ways of managing these problems are important to take into account, since targeting these problems may be beneficial for both parents and their children.

Although we evaluated numerous and various determinants, there may still be other mechanisms contributing to behavioral problems. Muriel et al found family psychiatric history as a risk factor of steroid-induced affective symptoms in a cohort of 125 patients with ALL.[43] In the general population, factors such as recent parental unemployment or divorce increased the risk of behavioral or emotional

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.

problems in children.[44] In pediatric patients with cancer, cumulative exposure to stressful life events was associated with symptoms of depression and anxiety.[38] Screening for family problems and life events, for example, with the psychosocial assessment tool (PAT),[45] may therefore be valuable to identify patients and families at risk of (steroid-induced) behavioral problems.

For parent-reported dexamethasone-induced sleep problems, no other determinants besides parenting stress were identified. In the general population and in childhood cancer survivors, female sex is a known risk factor for sleep disturbances.[46,47] We did not find a difference between boys and girls, which may be due to the young age of our cohort, as puberty and hormonal factors seem to play an important role in sex differences of sleep problems.[47] Other factors that could contribute to (dexamethasone-induced) sleep problems, such as sleep hygiene, comorbidities, and pain,[14,48] were unfortunately not available in our cohort.

There was no significant contribution of genetic variation, by exploring carrier status of two most relevant reported candidate SNPs, on dexamethasone-induced neurobehavioral and sleep problems. This may be due to our relatively small cohort for exploring genetic variation. Prior work described the advantage of combining genetic variants to study their effects on brain structure and function, while solitary SNPs may not be associated, especially on individual level.[49,50] Studying these combined genetic variants or performing a genome-wide association study in a sufficiently large cohort could be of value to detect patients with an inborn increased risk for steroid-induced side effects. We did not find an association between behavioral or sleep problems and dexamethasone pharmacokinetics as well; however, we only measured one peak and one trough level, and a more extensive pharmacokinetic(-pharmacodynamic) model, including more time points, may give more insight in the differences in dexamethasone clearance and side effects in patients.

Although parenting strategies were not systematically evaluated and the qualitative responses in our study were meant to gain insight in the ways of managing dexamethasone-induced problems by parents, 25% of the parents spontaneously indicated that they wielded lax(er) parenting strategies during the dexamethasone courses. Interestingly, previous studies showed that parental laxness and inconsistent discipline are associated with increased behavioral and emotional difficulties, as well as parent-reported child sleep problems, in patients with ALL.[51,52,53] Therefore, we anticipate that parenting strategies may be a modifiable target for health care providers, thereby improving child behavioral and sleep outcomes. Given the independent value of this factor, we feel that future studies may include systematic evaluation of parenting strategies in order to design successful interventions.

The main strength of our study is the fact that we were able to invite all eligible patients with ALL due to our national centralized pediatric cancer care. The included study population was representative and, to our knowledge, the largest prospective series to date. We were also able to study a broad range of possible determinants. Limitations are risk of bias in inclusion, as families of patients who experience more dexamethasone-induced side effects may have been more interested to participate. Besides, it may be possible that certain predisposing factors, for example, differences in dexamethasone kinetics, were not found to be significantly associated with the outcomes because of the relatively small sample size. Additionally, the study was not primarily powered for the multivariable analyses. Our results are based on proxy reports, since most included patients were too young to fill in questionnaires themselves. Only 19 children were age 11 years and older and therefore offered the SDQ self-report. When comparing the delta SDQ of the 12 patients who completed the SDQ on both time points with their parents, we found a poor agreement between these scores. It has been described before that parents and children report side effects differently.[54,55] The group of patients who were able to complete a self-report was very small; therefore, no conclusions regarding determinants could be made. The use of proxy reports may also be an explanation for the fact that we only found parental factors to be associated with the reported outcomes.

To conclude, we identified parenting stress during dexamethasone as a determinant for parent-reported neurobehavioral and sleep problems, which may be a modifiable target. Future studies including larger cohorts that incorporate other possible risk factors such as coping with stress, (family) psychiatric history, stressful life events and parenting strategies, as well as more extensive genetic evaluation, may be of value.

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.

AFFILIATIONS

[1]Pediatric Oncology, Princess Máxima Center, Utrecht, the Netherlands
[2]Department of Hospital Pharmacy, Erasmus Medical Center, Rotterdam, the Netherlands
[3]Division of Endocrinology, Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands
[4]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, the Netherlands
[5]Mathematical Institute, Leiden University, Leiden, the Netherlands
[6]Department of Biomedical Data Science, Medical Statistics, Leiden University Medical Centre, Leiden, the Netherlands
[7]Department of Pediatric Endocrinology, Erasmus MC- Sophia Children's Hospital, Rotterdam, the Netherlands
[8]Child Health, UMCU-Wilhelmina Children's Hospital, Utrecht, the Netherlands

CORRESPONDING AUTHOR

Annelienke M. van Hulst, MD, Princess Maxima Center, Heidelberglaan 25, 3584 CS Utrecht, the Netherlands; e-mail: a.vanhulst@prinsesmaximacentrum.nl.

EQUAL CONTRIBUTION

E.L.T.v.d.A. and M.M.v.d.H.-E. contributed equally to this work.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/PO.22.00678.

AUTHOR CONTRIBUTIONS

Conception and design: Annelienke M. van Hulst, Martha A. Grootenhuis, Erica L. T. van den Akker, Marry M. van den Heuvel-Eibrink
Administrative support: Annelienke M. van Hulst
Provision of study materials or patients: Annelienke M. van Hulst, Rob Pieters, Marry M. van den Heuvel-Eibrink
Collection and assembly of data: Annelienke M. van Hulst, Emma J. Verwaaijen, Bertrand D. van Zelst, Linda Broer
Data analysis and interpretation: Annelienke M. van Hulst, Martha A. Grootenhuis, Emma J. Verwaaijen, Raphaële R. L. van Litsenburg, Letao Li, Rob Pieters, Marta Fiocco, Saskia M. F. Pluijm, Erica L. T. van den Akker, Marry M. van den Heuvel-Eibrink
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to http://www.asco.org/rwc or https://ascopubs.org/po/author-center.
Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Rob Pieters
Honoraria: Jazz Pharmaceuticals, Kite, a Gilead company, Novartis, Servier/Pfizer
Consulting or Advisory Role: Kite, a Gilead company, Jazz Pharmaceuticals, Servier
Travel, Accommodations, Expenses: Kite, a Gilead company, Jazz Pharmaceuticals, Servier

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors would like to thank all patients and parents who participated in this study, and all on-site personnel who contributed. The authors acknowledge KiKa for funding this study (project number 268) and http://www.dewonderlijkereis.nl for the ongoing donation to research on dexamethasone-induced side effects. The authors also acknowledge Dr. Ria Koolma for database support and Dr. Femke Verwer for supporting the management of the trial.

REFERENCES

1. Veerman AJ, Kamps WA, van den Berg H, et al: Dexamethasone-based therapy for childhood acute lymphoblastic leukaemia: Results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997-2004). Lancet Oncol 10:957-966, 2009
2. Vrooman LM, Stevenson KE, Supko JG, et al: Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: Results from a randomized study—Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. J Clin Oncol 31:1202-1210, 2013
3. Bostrom BC, Sensel MR, Sather HN, et al: Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: A report from the Children's Cancer Group. Blood 101:3809-3817, 2003
4. McGrath P, Pitcher L: Enough is enough': Qualitative findings on the impact of dexamethasone during reinduction/consolidation for paediatric acute lymphoblastic leukaemia. Support Care Cancer 10:146-155, 2002
5. McGrath P, Rawson-Huff N: Corticosteroids during continuation therapy for acute lymphoblastic leukemia: The psycho-social impact. Issues Compr Pediatr Nurs 33:5-19, 2010
6. Pound CM, Clark C, Ni A, et al: Corticosteroids, behavior, and quality of life in children treated for acute lymphoblastic leukemia; a multicentered trial. J Pediatr Hematol Oncol 34:517-523, 2012
7. Aljebab F, Choonara I, Conroy S: Systematic review of the toxicity of long-course oral corticosteroids in children. PLoS One 12:e0170259, 2017
8. Hochhauser CJ, Lewis M, Kamen BA, et al: Steroid-induced alterations of mood and behavior in children during treatment for acute lymphoblastic leukemia. Support Care Cancer 13:967-974, 2005
9. Stuart FA, Segal TY, Keady S: Adverse psychological effects of corticosteroids in children and adolescents. Arch Dis Child 90:500-506, 2005
10. Warris LT, van den Heuvel-Eibrink MM, den Hoed MA, et al: Does dexamethasone induce more neuropsychological side effects than prednisone in pediatric acute lymphoblastic leukemia? A systematic review. Pediatr Blood Cancer 61:1313-1318, 2014
11. Warris LT, van den Heuvel-Eibrink MM, Aarsen FK, et al: Hydrocortisone as an intervention for dexamethasone-induced adverse effects in pediatric patients with acute lymphoblastic leukemia: Results of a double-blind, randomized controlled trial. J Clin Oncol 34:2287-2293, 2016
12. Zupanec S, Jones H, Stremler R: Sleep habits and fatigue of children receiving maintenance chemotherapy for ALL and their parents. J Pediatr Oncol Nurs 27:217-228, 2010
13. Rosen G, Harris AK, Liu M, et al: The effects of dexamethasone on sleep in young children with acute lymphoblastic leukemia. Sleep Med 16:503-509, 2015
14. Sheikh IN, Roth M, Stavinoha PL: Prevalence of sleep disturbances in pediatric cancer patients and their diagnosis and management. Children (Basel) 8:1100, 2021
15. Hulst AM, Peersmann SHM, Akker ELT, et al: Risk factors for steroid-induced adverse psychological reactions and sleep problems in pediatric acute lymphoblastic leukemia: A systematic review. Psychooncology 30:1009-1028, 2021
16. Manenschijn L, van den Akker EL, Lamberts SW, et al: Clinical features associated with glucocorticoid receptor polymorphisms. An overview. Ann N Y Acad Sci 1179:179-198, 2009
17. Spijker AT, van Rossum EF: Glucocorticoid receptor polymorphisms in major depression. Focus on glucocorticoid sensitivity and neurocognitive functioning. Ann N Y Acad Sci 1179:199-215, 2009
18. Kaymak Cihan M, Karabulut HG, Yurur Kutlay N, et al: Association between N363S and BclI polymorphisms of the glucocorticoid receptor gene (NR3C1) and glucocorticoid side effects during childhood acute lymphoblastic leukemia treatment. Turk J Haematol 34:151-158, 2017
19. Vallance K, Liu W, Mandrell BN, et al: Mechanisms of dexamethasone-induced disturbed sleep and fatigue in paediatric patients receiving treatment for ALL. Eur J Cancer 46:1848-1855, 2010
20. Ismail MF, Lavelle C, Cassidy EM: Steroid-induced mental disorders in cancer patients: A systematic review. Future Oncol 13:2719-2731, 2017
21. Yang L, Panetta JC, Cai X, et al: Asparaginase may influence dexamethasone pharmacokinetics in acute lymphoblastic leukemia. J Clin Oncol 26:1932-1939, 2008
22. van Hulst AM, Verwaaijen EJ, Fiocco MF, et al: Study protocol: DexaDays-2, hydrocortisone for treatment of dexamethasone-induced neurobehavioral side effects in pediatric leukemia patients: A double-blind placebo controlled randomized intervention study with cross-over design. BMC Pediatr 21:427, 2021
23. Goodman R: The strengths and difficulties questionnaire: A research note. J Child Psychol Psychiatry 38:581-586, 1997
24. Goodman R: Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry 40:1337-1345, 2001
25. Maurice-Stam H, Haverman L, Splinter A, et al: Dutch norms for the Strengths and Difficulties Questionnaire (SDQ) - parent form for children aged 2-18 years. Health Qual Life Outcomes 16:123, 2018
26. Muris P, Meesters C, van den Berg F: The strengths and difficulties questionnaire (SDQ). Eur Child Adolesc Psychiatry 12:1-8, 2003
27. van Widenfelt BM, Goedhart AW, Treffers PD, et al: Dutch version of the strengths and difficulties questionnaire (SDQ). Eur Child Adolesc Psychiatry 12:281-289, 2003

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.

28. Bruni O, Ottaviano S, Guidetti V, et al: The Sleep Disturbance Scale for Children (SDSC). Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J Sleep Res 5:251-261, 1996
29. Romeo DM, Bruni O, Brogna C, et al: Application of the sleep disturbance scale for children (SDSC) in preschool age. Eur J Paediatric Neurol 17:374-382, 2013
30. De Brock AJVAA, Gerris JR, Abadin RR: NOSI Nijmeegse Ouderlijke Stress Index. Meetinstrument voor de vaststelling van stress bij opvoeders. Een uitgebreide versie (NOSI) voor psychodiagnostische doeleinden en een verkorte versie (NOSIK) voor signaleringsdoeleinden. Lisse, the Netherlands, Swets & Zeitlinger, 1992
31. Abidin RR: Parenting Stress Index. Charlottesville, VA, Pediatric Psychology Press, 1990
32. van Oers HA, Schepers SA, Grootenhuis MA, et al: Dutch normative data and psychometric properties for the Distress Thermometer for Parents. Qual Life Res 26:177-182, 2017
33. Drigan R, Spirito A, Gelber RD: Behavioral effects of corticosteroids in children with acute lymphoblastic leukemia. Med Pediatr Oncol 20:13-21, 1992
34. Mitchell CD, Richards SM, Kinsey SE, et al: Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: Results of the UK Medical Research Council ALL97 randomized trial. Br J Haematol 129:734-745, 2005
35. Myers RM, Balsamo L, Lu X, et al: A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia: A report from the Children's Oncology Group. Cancer 120:1417-1425, 2014
36. Hooke MC, Hatch D, Hockenberry MJ, et al: The longitudinal parallel process analysis of biomarkers of oxidative stress, symptom clusters, and cognitive function in children with leukemia. J Pediatr Oncol Nurs 37:244-254, 2020
37. Tabachnick BG, Fidell LS: Using Multivariate Statistics (ed 6). Harlow, United Kingdom, Pearson, 2014, pp 1055
38. Okado Y, Long AM, Phipps S: Association between parent and child distress and the moderating effects of life events in families with and without a history of pediatric cancer. J Pediatr Psychol 39: 1049-1060, 2014
39. Sint Nicolaas SM, Hoogerbrugge PM, van den Bergh EM, et al: Predicting trajectories of behavioral adjustment in children diagnosed with acute lymphoblastic leukemia. Support Care Cancer 24: 4503-4513, 2016
40. van der Geest IM, van den Heuvel-Eibrink MM, Passchier J, et al: Parenting stress as a mediator of parents' negative mood state and behavior problems in children with newly diagnosed cancer. Psycho-Oncology 23:758-765, 2014
41. Fedele DA, Hullmann SE, Chaffin M, et al: Impact of a parent-based interdisciplinary intervention for mothers on adjustment in children newly diagnosed with cancer. J Pediatr Psychol 38:531-540, 2013
42. Williams LK, McCarthy MC, Burke K, et al: Addressing behavioral impacts of childhood leukemia: A feasibility pilot randomized controlled trial of a group videoconferencing parenting intervention. Eur J Oncol Nurs 24:61-69, 2016
43. Muriel AC, Burgers DE, Treyball AN, et al: Risk factors for steroid-induced affective disorder in children with leukemia. Pediatr Blood Cancer 68:e28847, 2021
44. Harland P, Reijneveld SA, Brugman E, et al: Family factors and life events as risk factors for behavioural and emotional problems in children. Eur Child Adolesc Psychiatry 11:176-184, 2002
45. Pai AL, Patino-Fernandez AM, McSherry M, et al: The psychosocial assessment tool (PAT2.0): Psychometric properties of a screener for psychosocial distress in families of children newly diagnosed with cancer. J Pediatr Psychol 33:50-62, 2008
46. Peersmann SHM, Grootenhuis MA, van Straten A, et al: Insomnia symptoms and daytime fatigue co-occurrence in adolescent and young adult childhood cancer patients in follow-up after treatment: Prevalence and associated risk factors. Cancers (Basel) 14:3316, 2022
47. Suh S, Cho N, Zhang J: Sex differences in insomnia: From epidemiology and etiology to intervention. Curr Psychiatry Rep 20:69, 2018
48. Walter LM, Nixon GM, Davey MJ, et al: Sleep and fatigue in pediatric oncology: A review of the literature. Sleep Med Rev 24:71-82, 2015
49. Nikolova YS, Ferrell RE, Manuck SB, et al: Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. Neuropsychopharmacology 36:1940-1947, 2011
50. Pagliaccio D, Luby JL, Bogdan R, et al: Amygdala functional connectivity, HPA axis genetic variation, and life stress in children and relations to anxiety and emotion regulation. J Abnorm Psychol 124:817-833, 2015
51. Williams LK, Lamb KE, McCarthy MC: Behavioral side effects of pediatric acute lymphoblastic leukemia treatment: The role of parenting strategies. Pediatr Blood Cancer 61:2065-2070, 2014
52. McCarthy MC, Bastiani J, Williams LK: Are parenting behaviors associated with child sleep problems during treatment for acute lymphoblastic leukemia? Cancer Med 5:1473-1480, 2016
53. Rensen N, Steur LMH, Grootenhuis MA, et al: Parental functioning during maintenance treatment for childhood acute lymphoblastic leukemia: Effects of treatment intensity and dexamethasone pulses. Pediatr Blood Cancer 67:e28697, 2020
54. Kawabe K, Horiuchi F, Uno H, et al: Parent-adolescent agreement on adolescents' emotional and behavioral problems assessed by the strengths and difficulties questionnaire. Glob Pediatr Health 8:2333794X2110012, 2021
55. Roeser K, Eichholz R, Schwerdtle B, et al: Relationship of sleep quality and health-related quality of life in adolescents according to self- and proxy ratings: A questionnaire survey. Front Psychiatry 3:76, 2012

Downloaded from ascopubs.org by 86.84.197.165 on May 21, 2025 from 086.084.197.165
Copyright © 2025 American Society of Clinical Oncology. All rights reserved.