Multidisciplinary interventions for attention deficits in paediatric cancer - a systematic review

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Introduction

Upto **80%**

More under-18s with cancer now survive into adulthood.

They often need long-term follow-up for physical and psychiatric late effects.

1/3

Some cancer survivors sustain cognitive deficits, particularly impaired attention.

Long-term neurodevelopmental effects of paediatric cancer are not clear.

?Clinical relevance

Current interventions are modelled on Attention-Deficit Hyperactivity Disorder (medication and cognitive training).

This approach may not be effective across paediatric cancer sample, where various attention deficits precede cognitive decline.

Early intervention and monitoring strategies could prevent or reduce cognitive decline.

Aim

To evaluate the impact of the following interventions on attention deficits in patients diagnosed with cancer at < 18 years old -

a. **neuropsychological interventions.**
b. **pharmacological treatments.**

This systematic review updates the evidence for cognitive interventions in this cohort – as the last review was published in 2014.

There is more focus on attention deficits, which could be key to early intervention.

The International Cognition and Cancer Task Force highlighted that neuroscientific understanding of cancer-related cognitive impairment was limited.

Previous reviews commented on the lack of consistent evidence for cognitive interventions, or their long-term effectiveness.

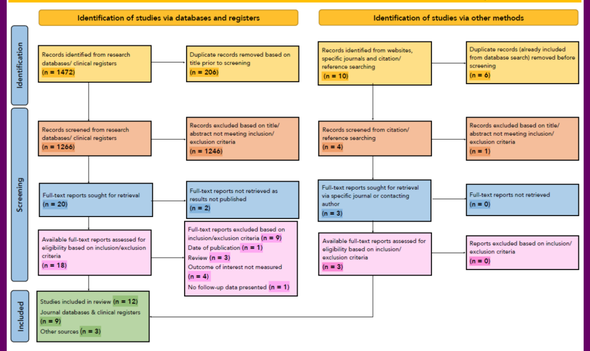
Methods

Process: Inclusion/ exclusion criteria (Figure 1) used to search information sources (Figure 2).

Figure 1 – Inclusion and exclusion criteria for studies

PICO framework	Eligibility criteria
Population	Historical or ongoing cancer diagnosis under the age of 18. Studies excluded if; a) sample did not include paediatric cancer patients/ survivors b) majority of the sample > 18 years old (adults)
Intervention	a) Psychological therapies b) Pharmacological interventions
Comparison	Patients within the same demographic as the sample population who were receiving; a) treatment as usual, or b) on the waiting list for standard treatment
Outcome	Primary outcome; measured empirically by neuropsychological testing Changes in attention span or observed attention deficits Secondary outcomes; recorded using patient or collateral reports a) Overall intelligence quotient (IQ) b) Academic achievement c) Social wellness and adaptive functioning Studies excluded if their primary/ secondary outcomes did not evaluate or report attention deficits
Additional exclusion criteria; a) Studies published prior to 2013 b) Study design - systematic reviews, meta-analyses, editorial articles, conference abstracts, case studies. c) Studies reported without an English translation. d) Full-text version unavailable. e) Outcome data not published.	

Figure 2 – Information sources, Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)



Mixed Methods Appraisal Tool (MMAT): critical appraisal tool used to appraise methodological research quality.

Identified the following issues -

a. unclear randomisation method (1 study).

b. limited outcome data (1 study).

c. absent/ unclear assessor blinding (2 studies).

d. less than 80% adherence with intervention (2 studies).

Results

Figure 3 – Study characteristics

Study	Methodology	Sample (Size = diagnosis, age)	Intervention	Measures
Cognitive &/ exercise training				
Ruiter et al. (2016)	RCT	80 = PBS, 8 - 18	Neurofeedback	ANT & SWAN
Carlson-Green, Puig and Bendel (2016)	Pre-post	20 = PBS, 8 - 18	Cogmed	CBCL
Conklin et al. (2015)	RCT	68 = PBS/ALLS, 8 - 16	Cogmed	CPT-II & CPRS-3
Conklin et al. (2016)	RCT (6 month followup)	68 = PBS/ALLS, 8 - 16	Cogmed	CPT-II & CPRS-3
Hardy et al. (2013)	RCT	20 = PBS/ALLS, 8 - 16	Cogmed	WRAML-2 & CPRS-3
Mendoza et al. (2019)	RCT	68 = PBS/ALLS, 8 - 16	Cogmed	CPRS-3 & WISC-IV
Siciliano et al. (2021)	RCT	41 = PBD, 7 - 16	Cogmed (adaptive vs non-adaptive)	NTCB & CBCL
Benzing et al. (2020)	RCT	70 = PCS (+CNS), 7 - 16	Cogmed Exergaming (Shape Up)	WISC-IV
Riggs et al. (2016)	Non-RCT (crossover)	28 = PBS, 6 - 17	Exercise training	CANTAB
Sabel et al. (2016)	RCT (crossover)	13 = PBS, 7 - 17	Nintendo Wii©	CPT-II, Map mission & D-KEFS
Psychological therapies				
Abedini et al. (2020)	RCT	40 = Cancer diagnosis (except CNS), 11 - 13	MBCT-C	CBCL & YSR
Pharmacological interventions				
Ayoub et al. (2020)	RCT (crossover)	24 = PBS, 5 - 21	Metformin	CANTAB

Figure 4 – Summary of results

8 Cognitive training studies - Neurofeedback (1), Cogmed (7 - including 1 versus Exergaming)

Cogmed - attention significantly improved (3 out of 7 studies), not maintained at 6 month follow-up

Neurofeedback - no significant effect on attention

3 Physical training studies - Exergaming vs Cogmed, Exercise training & Nintendo Wii©

Exergaming - no significant changes, or differences with Cogmed

Exercise training - significant improvement in attention after intensive group training

Nintendo Wii© - no improvement in attention

1 Psychotherapy study - MBCT-C (Mindfulness Based Cognitive Therapy for Children)

Significant improvement in attention self-reported by patients and caregivers during ongoing cancer treatment

1 Medication study - Metformin (typically used in Diabetes Type 2 management)

Significant improvement in attention observed in paediatric brain cancer survivors

Research focusing on this area of clinical need is limited, with few replicable studies

Figure 5 – Research limitations

Heterogeneity

Measures - no standardised cognitive outcomes

Clinical status - effects of various primary cancers, tumour spread to other sites, and different exposures to treatment not considered

Development

Age - no differences in treatment response considered between children and adolescents

Baseline - pre-morbid features (e.g. ADHD) typically excluded, affecting generalisability

Limited data

Long-term - no data beyond 6 months, could not consider if changes/ relapse affected outcomes

Co-morbidities - endocrine/ neuropsychiatric effects on cognitive function not considered

Confounders

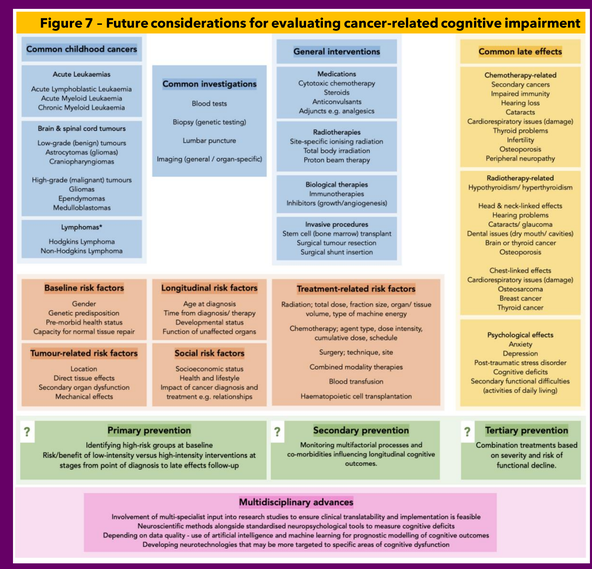
Physical - impact of interventions on common issues (e.g. pain/ fatigue/ sleep) not considered

Psychosocial - role of therapies in addressing anxiety (linked to cognition) not clearly defined

Figure 6 – Limitations of clinical translatability

Primary prevention	Secondary prevention	Tertiary prevention
Identifying possible high-risk groups	**Cognitive risk monitoring targets**	**Considering treatment limitations**
Early childhood cancer onset	Cancer spread or relapse	Particular age groups
ADHD/ neurodisability	Endocrine dysfunction	Global developmental delay
Systemic (pain/ fatigue/ sleep)	Neurological sequelae	Active treatment vs remission
Anxiety/ depression	Chemoradiotherapy-related impairments	Adjunct to palliative care
Risk-targeted cognitive interventions	Multiple treatment episodes	**Combining cognitive interventions**
Low-intensity support for low-risk cases e.g. sleep hygiene	Posterior Fossa Syndrome (PFS)	Interacting cognitive risk factors e.g. pain & depression
High-intensity input for high-risk cases e.g. Cogmed	Post-traumatic stress disorder	Cumulative risk factors e.g. baseline ADHD with PFS

Figure 7 – Future considerations for evaluating cancer-related cognitive impairment



Conclusion

Ways in which research could evolve to target cancer-related cognitive impairment:

1. **Neurodevelopment** - define cognitive effects of different cancer types/ co-morbidities/ treatments.
2. **Standardised measures** - cognitive risk assessment & prognostic models e.g. corroborate risk factors large clinical datasets.
3. **Targeted cognitive interventions** – for specific areas of cognitive dysfunction or cognitive risk factors.

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