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EDITORIALS

Melatonin in children with cancer

Unsupported claims of effectiveness are misleading families

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Recent calls have been made for young cancer patients to be given melatonin as part of NHS “standard of care” treatment. The premise is that melatonin “could save lives as well as the NHS money”—by improving survival and reducing adverse side effects.¹ This has generated understandable media interest.²

Cancer affects one in 500 people under the age of 14 and is a leading cause of death in childhood. It is highly emotive, with the potential to have devastating effects on the lives of affected families who, quite understandably, will go to extremes to support their children. Reassuringly, five and 10 year survival rates have doubled since the 1970s,³ with the increases being attributed to systematic and widespread adoption of collaborative clinical trials to evaluate new approaches to treatment.⁴

Although over 80% of young people who have cancer diagnosed will survive long term, six out of 10 will experience one or more serious late effects a decade after they completed treatment.⁵ Consequently, the search for approaches that increase survival while reducing short and long term morbidity, remains a priority.

Melatonin is an indolamine hormone produced by the pineal gland.^{6,7} Its main physiological role seems to be the regulation of circadian rhythms of sleep, with evidence that is effective in treating sleep disorders, including prevention and management of jetlag.⁸ In association with behavioural modification, it is used in the management of sleep disorders in children,⁹ including those with learning disabilities and those with disrupted sleep associated with brain tumours.¹⁰

Weak evidence

Melatonin’s antioxidant property is the basis for its potential to inhibit the growth of cancer cells, with studies *in vitro* and in animals suggesting antimetabolic or immunomodulatory effects.⁹ Melatonin has been tested as an anti-cancer adjunct in clinical trials in patients with many different cancers, though only one trial was in children. The trials have been drawn together in multiple systematic reviews,¹⁰ which have highlighted the need for stronger evidence of benefit. These reviews often comment on the moderate to high risk of bias in underlying trials as well

as their heterogeneity. Such weaknesses make pooled estimates drawn from meta-analysis unreliable and potentially misleading.¹¹ A clear understanding of the limitations of systematic reviews is essential when interpreting their findings. Plain English summaries of findings, including appropriate caution and signposting to other patient resources, may help to minimise misinterpretation and any attendant distress.

The only study of melatonin in children with cancer is a preliminary (phase I) dose finding study, intended primarily to identify an appropriate dose for further investigation.¹² This study has been presented as a conference abstract but not yet published in a peer reviewed journal. It showed tolerability, but side effects included nausea, anorexia, dizziness, fatigue, rashes, and weight changes. Notably, children being treated with anthracyclines, a widely used class of anti-cancer drugs in young people, were excluded because of concerns about the possible harmful interaction with such chemotherapy.

The media coverage surrounding the use of melatonin has provoked, in equal measure, interest and concern from families affected by childhood cancer. Many parents have been left wondering if they should give melatonin alongside their child’s treatment and are concerned that information about this supplement was not available to them earlier. Medical and nursing professionals in the UK and Ireland believe there is insufficient evidence to endorse widespread use of melatonin by children with cancer at this stage¹³ and that claims of effectiveness are misleading to families.

Inadequately supported statements from widely trusted sources may lead families to use melatonin without informing medical professionals. Such statements may cause additional distress to families, who are already under immense pressure. As we strive to offer hope and support to families affected by childhood cancer, all individuals and organisations should exercise responsible caution to avoid unintentionally compounding distress and harm through premature claims of treatment benefits, particularly improved survival.

The evidence for melatonin's use as an anti-cancer agent is currently weak, and in children effectively non-existent. The proposal to introduce melatonin as "standard of care" in young people with cancer is not supportable. Robust evidence from carefully designed and conducted clinical trials must underpin all treatments for cancer in young people, and melatonin is no exception.

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Provenance and peer review: Not commissioned; externally peer reviewed.

- 1 Children with Cancer (UK). Melatonin supplement 2018 <https://www.childrenwithcancer.org.uk/stories/melatonin-supplement/>
- 2 Charity calls for NHS to use jetlag supplement. *Daily Mail* 2018 Sep 14. <https://www.dailymail.co.uk/health/article-6164793/Charity-calls-NHS-children-cancer-1-jetlag-supplement.html>
- 3 Cancer Research UK. Cancer stats 2018. <https://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/survival#heading-Two>
- 4 Stiller CA, Kroll ME, Pritchard-Jones K. Population survival from childhood cancer in Britain during 1978-2005 by eras of entry to clinical trials. *Ann Oncol* 2012;23:2464-9. . 10.1093/annonc/mds183 22811513

- 5 Oeffinger KC, Mertens AC, Sklar CA, et al. Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006;355:1572-82. 10.1056/NEJMsa060185 17035650
- 6 Reppert SM, Weaver DR. Melatonin madness. *Cell* 1995;83:1059-62. 10.1016/0092-8674(95)90131-0 8548792
- 7 Brzezinski A. Melatonin in humans. *N Engl J Med* 1997;336:186-95. 10.1056/NEJM199701163360306 8988899
- 8 Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev* 2002;2:CD001520. 10.1002/14651858.CD001520. 12076414
- 9 Karbownik M, Reiter RJ. Antioxidative effects of melatonin in protection against cellular damage caused by ionizing radiation. *Proc Soc Exp Biol Med* 2000;225:9-22. 10.1046/j.1525-1373.2000.22502.x 10998194
- 10 Posadzki PP, Bajpai R, Kyaw BM, et al. Melatonin and health: an umbrella review of health outcomes and biological mechanisms of action. *BMC Med* 2018;16:18. 10.1186/s12916-017-1000-8 29397794
- 11 Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002. 10.1136/bmj.d4002 21784880
- 12 Johnston D, Zupanec S, Nicksy D, et al. Phase I dose finding study for melatonin in paediatric oncology patients with relapsed solid tumors. *J Clin Oncol* 2018;36(suppl):e22514. 10.1200/JCO.2018.36.15_suppl.e22514.
- 13 Children's Cancer and Leukaemia Group Executive. Behind the headlines: melatonin and cancer. 2018. <https://www.cclg.org.uk/news/behind-the-headlines-melatonin-and-childhood-cancer>

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