

# Less Is More: Polypharmacy at the End of Life

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The World Health Organization describes polypharmacy as, “the administration of many drugs at the same time or the administration of an excessive number of drugs” [1]. While the quantifiable definition varies widely, the term can have both a positive and negative connotation. Appropriate and problematic polypharmacy is applicable for both adult and pediatric patients [2,3]. In the context of the dying patient, administration of polypharmacy may be appropriate, for example when treating a reversible life-threatening condition, but may be inappropriate when administered at end-of-life conditions.

Polypharmacy and patterns of aggressive end-of-life (EOL) care, especially the administration of chemotherapies, have been described in the adult cancer population, addressing the delicate balance between palliative symptom control, life prolongation, and severe side effects. Many of these studies have indicated a significant correlation between the number of medications administered and higher symptom burden and lower quality-of-life (QOL) [4-6].

A particular example of aggressive care at the EOL is the administration of chemotherapy in the last 30 days of life, which is considered futile and represents a widely accepted index of poor-quality cancer services [7-9]. Thus, the Choosing Wisely initiative, endorsed by the American Association of Clinical Oncology

(ASCO) specifically states: “Don’t use cancer-directed therapy for solid tumor patients with low performance status (Eastern Cooperative Oncology Group score of 3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anti-cancer treatment” [10].

In pediatric oncology, polypharmacy and optimal EOL care are not as well described compared to adults. Hospice care referrals, deaths in intensive care units (ICUs), and medication burden constitute the main parameters evaluating EOL quality of care and are in part adapted from the indicators developed by Earle et al. [8]. However, in the last two decades there has been a growing understanding of the necessity, importance, and uniqueness of pediatric palliative and EOL care. Due to this awareness, different training programs for palliative teams and oncologists were initiated. Several nation-wide studies were conducted for descriptive purposes and to evaluate improvement in key domains of quality-care for children near death [11-13].

In this issue of *Israeli Medical Association Journal (IMAJ)*, Tamir and colleagues [14], addressed the topic of polypharmacy among pediatric cancer patients dying in the hospital and report real-world data from a single institution in Israel. Among 90 children with hematologic, solid, or primary central nervous system malignancies, the median number of medication orders per patient remained consistent from the first day of hospitalization until the day of death, with a significantly higher medication burden observed among patients

with hematologic malignancies compared to the solid and CNS malignancies subgroups (median 6, 4, and 4, respectively;  $P = 0.006$ ). Possibly limited by the relatively small group of participants, the authors did not demonstrate a statistical association between other clinical and demographic parameters and medication burden, but interesting trends were observed. Notably, patient status as do-not-resuscitate (DNR) was associated with the curtailment of medications prescribed ( $P = 0.068$ ) and reduced rates of deaths in the ICU. Prompting early documentation of DNR orders may result in improved advanced care planning as previously proposed [11].

While Tamir et al. [14] did not differentiate between appropriate and inappropriate polypharmacy or describe indications for hospitalization (disease progression vs. treatment complication), the medication subgroup analysis revealed a general increase of prescriptions for opiates and anxiolytics, as would be the expected treatment approach in alleviation of multi-symptoms near death. More important, their data clearly suggest an association among diagnosis, prognosis, intent of therapy, and medication burden.

Treating cancer patients at the EOL situation is a complex issue, affected not only by clinical evidence but also by patient desires, wishes, and personal perspective. Despite ample literature and specific guidelines, including those of ASCO and Choosing Wisely, many patients continue to receive chemotherapy during their last days of life, providing minimal clinical benefit and potentially causing harm. This treatment approach occurs even more frequently among younger cancer

patients [15]. In pediatric oncology, the cessation of chemotherapy and withholding of medications may be a harder decision as a child's death is experienced as an occurrence against nature and is considered a tragedy. This topic was discussed at the international workshop on palliative care in Israel [16]. Nevertheless, Tamir et al. [14] observed a significant reduction in administration of chemotherapy ( $P = 0.035$ ) during the last hospitalization.

Interestingly, the authors mentioned the possible impact of the oncologist's personal experience on the medical management. In fact, studies of EOL care outline the difficulty of oncologists to engage in conversations of prognosis with their patients, which in time leads to a significant delay in a dialogue regarding choices, options, and perspectives of the terminally ill patient [17,18]. The decision to terminate oncologic treatment in favor of optimal palliative care is even harder with the expansion of therapeutic possibilities for advanced cancers, such as novel targeted therapies and immunotherapies, which may be less toxic. However, their influence on QOL near EOL has yet to be studied. Do these treatments provide a better therapy option in EOL care? We still do not know.

The issue of active treatment and polypharmacy in EOL care, either in adult and pediatric cancer patients, is extremely complex and involves much more than pure evidence-based data. Decisions taken at EOL must include a wide range of physical, social, and personal prospects and involve a process of shared decision making with all relevant partners, including the patient, family, physicians, nurses, social workers, and psychologists. Many questions remain to be answered regarding polypharmacy and aggressive EOL care: What are the current trends and practice patterns in Israel? Will the direction toward home-

based palliative and hospice care influence the intensity of treatment while on EOL care? Should novel targeted therapies and immunotherapies be regarded as the older chemotherapies or should we treat with these agents even at EOL? Last, should we consider polypharmacy and avoidance of chemotherapy near EOL as a national quality-care index in Israel?

**CONCLUSIONS**

End-of-life care is a sensitive and delicate setting for patients and families. Mistakes made by the clinical team at this point may be irreversible and cause unnecessary distress. It is important to address this complex scenario with continued research, education, and quality assurance, which may lead to the development of better medical practices. We owe better EOL care to our patients and to ourselves.

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**References**

1. WHO Centre for Health Development Ageing and Health Technical Report. A glossary of terms for community health care and services for older persons. WHO Centre for Health Development. Volume 5 2004. [Available from [http://apps.who.int/iris/bitstream/handle/10665/68896/WHO\\_WKC\\_Tech.Ser.\\_04.2.pdf;jsessionid=AD4215478C552D7D7498905C592EB9AA?sequence=1](http://apps.who.int/iris/bitstream/handle/10665/68896/WHO_WKC_Tech.Ser._04.2.pdf;jsessionid=AD4215478C552D7D7498905C592EB9AA?sequence=1)]. [Accessed 16 January].
2. Duerden M, Avery T, Payne R, Barnsteiner JH. Polypharmacy and medicines optimisation Making it safe and sound. In: Patient Safety and Quality: an Evidence-based Handbook for Nurses. London: The King's Fund, 2008. [Available from [https://www.kingsfund.org.uk/sites/default/files/field/field\\_publication\\_file/polypharmacy-and-medicines-optimisation-kingsfund-nov13.pdf](https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/polypharmacy-and-medicines-optimisation-kingsfund-nov13.pdf)].
3. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatrics* 2017; 17(1): 230.
4. Schenker Y, Park SY, Jeong K, et al. Associations between polypharmacy, symptom burden, and

- quality of life in patients with advanced, life-limiting illness. *J Gen Intern Med* 2019; 34 (4): 559-66.
5. McNeil MJ, Kamal AH, Kutner JS, Ritchie CS, Abernethy AP. The burden of polypharmacy in patients near the end of life. *J Pain Symptom Manage* 2016; 51 (2): 178-83.e2.
6. LeBlanc TW, McNeil MJ, Kamal AH, Currow DC, Abernethy AP. Polypharmacy in patients with advanced cancer and the role of medication discontinuation. *Lancet Oncol* 2015; 16 (7): e333-41.
7. Earle CC, Neville BA, Landrum MB, et al. Evaluating claims-based indicators of the intensity of end-of-life cancer care. *Int J Qual Heal Care* 2005; 17 (6): 505-9.
8. Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol* 2004; 22 (2): 315-21.
9. Massa I, Nanni O, Foca F, et al. Chemotherapy and palliative care near end-of life: Examining the appropriateness at a cancer institute for colorectal cancer patients. *BMC Palliat Care* 2018; 17 (1): 1-7.
10. ABIM Foundation. Choosing Wisely. Care at the end of life for advance cancer patients 2014. [Available <https://www.choosingwisely.org/societies/american-society-of-clinical-oncology/>]. [Accessed 16 January].
11. Wolfe J, Hammel JE, Edwards KE, Duncan J, Comeau M, Breyer J, et al. Easing of suffering in children with cancer at the end of life: Is care changing? *J Clin Oncol* 2008; 26 (10): 1717-23.
12. Zimmermann K, Cignacco E, Engberg S, et al. Patterns of paediatric end-of-life care: a chart review across different care settings in Switzerland. *BMC Pediatr* 2018; 18 (1): 1-10.
13. Tang ST, Hung YN, Liu TW, et al. Pediatric end-of-life care for Taiwanese children who died as a result of cancer from 2001 through 2006. *J Clin Oncol* 2011; 29 (7): 890-4.
14. Tamir S, Kurnik D, Weyl Ben-Arush M, Postovsky S. Polypharmacy among pediatric cancer patients dying in the hospital. *IMAJ* 2021; 426-31.
15. Zhang Z, Chen ML, Gu XL, Liu MH, Zhao WW, Cheng WW. Palliative chemotherapy near the end of life in oncology patients. *Am J Hosp Palliat Med* 2018; 35 (9): 1215-20.
16. Shaulov A, Baddarni K, Cherny N, Shaham D, Shvartzman P, Tellem R, Clarfield AM. "Death is inevitable - a bad death is not" report from an international workshop. *Isr J Health Policy Res* 2019; 8 (1): 79.
17. Harrington SE, Smith TJ. The role of chemotherapy at the end of life: "When is enough, enough?" *JAMA* 2008; 299 (22): 2667-78.
18. Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: Predictors and outcomes of receipt of care consistent with preferences. *J Clin Oncol* 2010; 28 (7): 1203-8.

**One is happy as a result of one's own efforts once one knows the necessary ingredients of happiness: simple tastes, a certain degree of courage, self denial to a point, love of work, and above all, a clear conscience.**

George Sand [pen name of Amantine-Aurore-Lucile Dupin] (1804-1876), novelist