

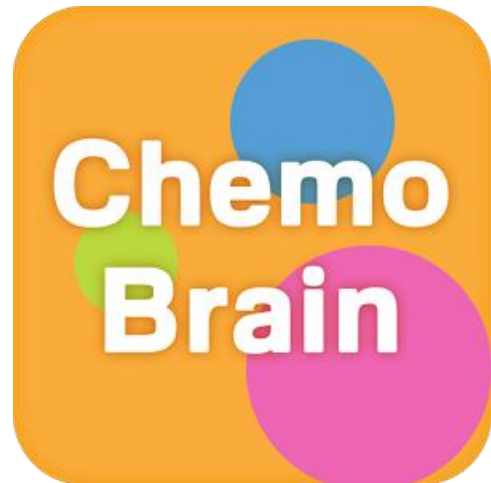
Cancer Association of South Africa (CANSA)



CANSA Fact Sheet on Chemo Brain

Introduction

Chemo brain, also known as post-chemotherapy cognitive impairment (PCCI), chemotherapy-induced cognitive dysfunction or impairment, or chemo fog, describes the cognitive impairment that can result from chemotherapy treatment. Approximately 20–30% of people who undergo chemotherapy experience some level of post-chemotherapy cognitive impairment. The phenomenon first came to light because of the large number of breast cancer survivors who complained of changes in memory, fluency, and other cognitive abilities that impeded their ability to function as they had pre-chemotherapy.



[Picture Credit: Chemo Brain]

Although the causes and existence of post-chemotherapy cognitive impairment has been a subject of debate, recent studies have confirmed that post-chemotherapy cognitive impairment is a real, measurable side effect of chemotherapy that appears in some patients. While any cancer patient may experience temporary cognitive impairment while undergoing chemotherapy, patients with PCCI continue to experience these symptoms long after chemotherapy has been completed. PCCI is often seen in patients treated for breast cancer, ovarian cancer, prostate cancer, and other reproductive cancers, as well as other types of cancers requiring aggressive treatment with chemotherapy.

The clinical relevance of PCCI is significant, considering the increasing number of long-term cancer survivors in the population, many of whom may have been treated with aggressive dosing of chemotherapeutic agents, or with chemotherapy as an adjuvant to other forms of treatment. In some patients, fear of PCCI can impact treatment decisions. The magnitude of chemotherapy-related cognitive changes and their impact on the activities of daily living are uncertain.

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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Post-chemotherapy Cognitive Impairment (PCCI)

Chemo brain is a common term used by cancer survivors to describe thinking and memory problems that can occur after cancer treatment. Chemo brain can also be called chemo fog, chemotherapy-related cognitive impairment or cognitive dysfunction.

Though chemo brain is a widely used term, it's misleading. It's unlikely that chemotherapy is the sole cause of concentration and memory problems in cancer survivors. Despite the many questions with regard to this problem, it is clear that the memory problems commonly called chemo brain can be a frustrating and debilitating side effect of cancer and its treatment. More study is needed to understand this condition.

Cancer patients have long complained of neurological side effects such as short-term memory loss and, in extreme cases, seizures, vision loss, and even dementia. Until very recently, these cognitive side effects were often dismissed as the by-product of fatigue, depression, and anxiety related to cancer diagnosis and treatment. Now a growing body of evidence has documented the scope of these conditions, collectively referred to as chemo brain. And while it is increasingly acknowledged by the scientific community that many chemotherapy agents may have a negative impact on brain function in a subset of cancer patients, the precise mechanisms that underlie this dysfunction have not been identified.

Virtually all cancer survivors experience short-term memory loss and difficulty concentrating during and shortly after treatment. A study two years ago by researchers with the James P. Wilmot Cancer Center at the University of Rochester showed that upwards of 82% of breast cancer patients reported that they suffer from some form of cognitive impairment.



[Picture Credit: Blame it on Chemo Brain]

While these effects tend to wear off over time, a subset of patients, particularly those who have been administered high doses of chemotherapy, begin to experience these cognitive side effects months or longer after treatment has ceased and the drugs have long since departed their systems. For example, a recent study estimates that somewhere between 15 and 20 percent of the nation's 2.4 million female breast cancer survivors have lingering cognitive problems years after treatment. Another study showed that 50 percent of women had not recovered their previous level of cognitive function one year after treatment.

Liu, P., Guo, L., Yu, X., Liu, P., Yu, Y., Kong, X., Yu, X., Zephania, H.M., Liu, P. & Huang, Y. 2023.

“Doxorubicin (DOX) is a cornerstone of chemotherapy for solid tumors and leukemias. DOX-induced cognitive impairment, termed chemo brain, has been reported in cancer survivors, whereas its mechanism remains poorly understood. Here we initially evaluated the cognitive impairments of mice treated with clinically relevant, long-term, low-dosage of DOX. Using HILIC-MS/MS-based targeted metabolomics, we presented the changes of 21 amino acids across six anatomical brain regions of mice with DOX-induced chemo brain. By mapping the altered amino acids to the human metabolic network, we constructed an amino acid-based network module for each brain region. We identified phenylalanine, tyrosine, methionine, and γ -aminobutyric acid as putative signatures of three regions (hippocampus, prefrontal cortex, and neocortex) highly associated with cognition. Relying on the reported mouse brain metabolome atlas, we found that DOX might perturb the amino acid homeostasis in multiple brain regions, similar to the changes in the aging brain. Correlation analysis

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[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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suggested the possible indirect neurotoxicity of DOX that altered the brain levels of phenylalanine, tyrosine, and methionine by causing metabolic disorders in the liver and kidney. In summary, we revealed the region-specific amino acid signatures as actionable targets for DOX-induced chemo brain, which might provide safer treatment and improve the quality of life among cancer survivors.”

ICD-10 Code for Cognitive Impairment

ICD-10 code **R41.84** for other specified cognitive deficit is a medical classification as listed by WHO under the range -Symptoms and signs involving co.

ICD-10 code **G31.84** for mild cognitive impairment of uncertain or unknown aetiology is a medical classification as listed by WHO under the range -Other.

N.B. There does not seem to be a specific ICD-10 code for Post-chemotherapy Cognitive Impairment (PCCI)

Causes of Post-chemotherapy Cognitive Impairment (PCCI)

It is still not clear what causes mild cognitive impairment.

Research suggests that there may be a number of factors that contribute to it, including:

Chemotherapy - so far, research has not clearly shown whether chemotherapy causes these thought and memory changes. Early studies only tested people after their chemotherapy. These tests showed that people had cognitive impairment. But more recent research has shown that some people with cancer have similar problems before they start any treatment and that the changes may even improve during treatment. This implies that it could be something to do with having cancer, rather than having cancer treatment. There are, however, many individuals complaining of post-chemotherapy cognitive impairment who are certain that they never had similar problems before their cancer treatment.

Other cancer treatments - many people have more than one type of treatment for cancer, which makes it difficult to work out what is causing a particular side effect. A small study looked at 31 women treated with the hormone therapies, tamoxifen and anastrozole. They found that women taking anastrozole had more thought and memory problems than women taking tamoxifen. Another study compared women taking tamoxifen with women taking exemestane and with women who had not had breast cancer. This study found that the women taking tamoxifen had more problems with memory and organisation skills than those taking exemestane and the women who hadn't had cancer. We need more research to find out what effects hormone therapy and other cancer treatments may have.

Anxiety, fatigue, old age, depression - from research, we know that people who report thought and memory problems after chemo are more likely to have anxiety and depression than people who don't have these symptoms. But it isn't clear whether one causes the other. There could be another factor that leads to thought and memory problems as well as anxiety and depression.

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

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Changes in blood proteins called cytokines - Cytokines are proteins made by the body as part of the immune response. Researchers have looked at blood levels of cytokines in women who had treatment for breast cancer. The researchers compared them with cytokine levels in women who didn't have breast cancer. They found that women with breast cancer had higher cytokine levels. They also found that women who reported thought and memory problems had the highest levels of cytokines. We need more research to find out what this actually means. The researchers are extending their study to include more women who have had breast cancer and also people with other types of cancer.

Signs and Symptoms of Post-chemotherapy Cognitive Impairment (PCCI)

Any person who has received cancer treatment and are experiencing the following types of problems, may be experiencing PCCI:

- Memory loss
- Trouble paying attention
- Short attention span
- Fumbling for the right word or phrase
- Difficulty with new learning
- Difficulty managing daily activities
- Difficulty concentrating on a single task
- Difficulty learning new skills
- Problems with short-term memory; forgetting details of recent events
- Feeling mentally 'slower' than usual
- Confusing dates and appointments
- Misplacing objects
- Being unusually disorganised
- Difficulty concentrating
- Difficulty multitasking
- Taking longer than usual to complete routine tasks
- Trouble with verbal memory, such as remembering a conversation
- Trouble with visual memory, such as recalling an image or list of words

People often notice these problems during chemotherapy treatment. Within one year of treatment, many people find these difficulties greatly improve or no longer exist. However, for some people, PCCI can continue for years following completion of treatment.

Preventing and Treating Post-chemotherapy Cognitive Impairment (PCCI)

Doctors have been looking into how to prevent and treat cancer related thought and memory problems. It is still too early to know how well these work but they include:

- Erythropoietin (EPO) – this drug may help by raising haemoglobin levels
- Aspirin – which works as a mild blood thinning drug

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[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

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- Methylphenidate – a type of stimulant for chronic fatigue syndrome, daytime drowsiness and attention deficit disorder

The aim with EPO or aspirin treatment is to maintain or increase blood flow to the brain cells and so increase their oxygen supply. Understanding more about what causes PCCI will help doctors to find ways of preventing and treating it.

Mahmoud, A.M.A., Mantawy, E.M., Wahdan, S.A., Ammar, R.M. & El-Demerdash, E. 2023.

“Cisplatin (CP) is a broad-spectrum antineoplastic agent used to treat many human cancers. Nonetheless, most patients receiving CP suffer from cognitive deficits, a phenomenon termed "chemo-brain". Recently, vildagliptin (Vilda), a DPP-4 inhibitor, has demonstrated promising neuroprotective properties against various neurological diseases. Therefore, the present study aims to investigate the potential neuroprotective properties of Vilda against CP-induced neurotoxicity and elucidate the underlying molecular mechanisms. Chemo-brain was induced in Sprague-Dawley rats by i.p injection of CP at a dose of 5 mg/kg once weekly for four weeks. Vilda was administered daily at a dose (10 mg/kg; P.O) for four weeks. The results revealed that Vilda restored the cognitive function impaired by CP, as assessed by the Morris water maze, Y-maze, and passive avoidance tests. Moreover, Vilda alleviated the CP-induced neurodegeneration, as shown by toluidine blue staining, besides markedly reduced amyloid plaque deposition, as evidenced by Congo red staining. Notably, Vilda boosted cholinergic neurotransmission through the downregulation of the acetylcholinesterase enzyme. In addition, the neuroprotective mechanisms of Vilda include diminishing oxidative stress by reducing MDA levels while raising GSH levels and SOD activity, repressing neuronal apoptosis as shown by elevated Bcl-2 levels together with diminished Bax and caspase-3 expressions, inhibiting neuroinflammation as shown by decreased GFAP expression, and finally boosting hippocampal neurogenesis and survival by upregulating expressions of BDNF and PCNA. These effects were mainly mediated by activating AMPK/Akt/CREB signaling cascades. In summary, Vilda can be considered a promising candidate for guarding against CP-induced chemo-brain and neurodegeneration, thus improving the quality of life of cancer patients.”

Conflict of interest statement

Declaration of Competing Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Coping with Post-chemotherapy Cognitive Impairment (PCCI)

Not many treatments for PCCI currently exist, although some patients may find relief from stimulants such as Ritalin®, commonly used to treat Attention Deficit Hyperactivity Disorder (ADHD). Ritalin can help improve mental focus, concentration and stamina in cancer patients.

People can use the following coping strategies to minimise the effects of PCCI:

- Exercise - even five minutes of mild to moderate activity may improve mental function
- Go for a walk
- Memory Aids - using a notebook, planner, cell phone, or list to keep track of things as they come to mind. A small recorder can also come in handy
- Also use your mobile phone, a calendar or daily planner to keep track of tasks, appointments, social commitments, birthdays etc
- Treat fatigue and sleep problems - these conditions can worsen PCCI symptoms
- Manage depression and anxiety - easing stress and elevating mood can ease PCCI symptoms

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- Minimise distractions - a more soundproof environment, like an office or a cubicle in a different location can decrease distractions and improve concentration in the workplace
- Do mental exercises, such as crosswords
- Listen to music
- Plan the day to do the things that need the most thinking when feeling one's best and more alert, e.g. in the mornings
- Set aside time each day to read and respond to emails.
- Get extra rest
- Use a calendar and write down important dates and information
- Use a pill box to keep track of medications
- Try to keep one's life as simple as possible
- Avoid trying to do too many things at the same time
- Keeping one's mind active may help – for example, doing crosswords, sudoku and puzzles
- If you are working and have your own office, close the door when you don't want to be interrupted
- Put personal items (e.g. wallet, keys) in a dedicated place at home and at work so you don't misplace them
- Let phone calls go through to your answering machine or voicemail. You can listen to them and think about how you will respond when you feel ready
- Do tasks one at a time rather than multi-tasking
- Get plenty of sleep and exercise. Deep sleep is important for memory and concentration, and getting some physical activity every day will help you sleep better

Medical Disclaimer

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Sources and References Consulted or Utilised

Abraham, E.H., Khan, B., Ling, E. & Bernstein, L.J. 2022. The Development and Evaluation of a Patient Educational Resource for Cancer-Related Cognitive Dysfunction. *J Cancer Educ.* 2022 Feb;37(1):111-119.

Bernstein, L.J., Edelstein, K., Sharma, A. & Alain, C. 2021. Chemo-brain: An activation likelihood estimation meta-analysis of functional magnetic resonance imaging studies. *Neurosci Biobehav Rev.* 2021 Nov;130:314-325.

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Blame it on Chemo Brain

http://preventdisease.com/news/12/011012_Cemo-Therapy-or-Poison-Shouldnt-Cancer-Treatment-Kill-Cancer-Without-Killing-You.shtml

Cancercare

http://www.cancercare.org/publications/72-cognitive_problems_after_chemotherapy

Cancer Council NSW

<http://www.cancercouncil.com.au/15307/b1000/living-well-after-cancer-45/living-well-after-cancer-treatment-side-effects/>

<http://www.cancercouncil.com.au/15307/b1000/living-well-after-cancer-45/living-well-after-cancer-treatment-side-effects/#cognitive>

Cancer Research UK

<http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/chemo-brain#other>

<http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/chemo-brain#treat>

Chung, N.C., Walker, A.K., Dhillon, H.M. & Vardy, J.L. 2018. Mechanisms and treatment for cancer- and chemotherapy-related cognitive impairment in survivors of non-CNS malignancies. *Oncology (Williston Park)*. 2018 Dec 17;32(12):591-8.

Durán-Gómez, N., López-Jurado, C.F., Nadal-Delgado, M., Pérez-Civantos, D., Guerrero-Martín, J. & Cáceres, M.C. 2022. Chemotherapy-Related Cognitive Impairment in Patients with Breast Cancer Based on Functional Assessment and NIRS Analysis. *J Clin Med*. 2022 Apr 23;11(9):2363.

Eide, S. & Feng, Z-P. 2020. Doxorubicin chemotherapy-induced “chemo-brain”: meta-analysis. *Eur J Pharmacol*. 2020 Aug 15;881:173078. doi: 10.1016/j.ejphar.2020.173078. Epub 2020 Jun 5.

Floyd, R., Dyer, A.H. & Kennelly, S.P. 2021. Non-pharmacological interventions for cognitive impairment in women with breast cancer post-chemotherapy: a systematic review. *J Geriatr Oncol*. 2021 Mar;12(2):173-181.

Juan, Z., Chen, J., Ding, B., Yongping, L., Liu, K., Wang, L., Le, Y., Liao, Q., Shi, J., Huang, J., Wu, Y., Ma, D., Ouyang, W. & Tong, J. 2022. Probiotic supplement attenuates chemotherapy-related cognitive impairment in patients with breast cancer: a randomised, double-blind, and placebo-controlled trial. *Eur J Cancer*. 2022 Jan;161:10-22.

Kovulchuk, A. & Kolb, B. 2017. Chemo brain: from discerning mechanisms to lifting the brain fog – an aging connection. *Cell Cycle*. 2017 Jul 18;16(14):1345-1349. doi: 10.1080/15384101.2017.1334022. Epub 2017 Jun 28.

Lange, M., Joly, J., Ahles, T., Dubois, M., Tron, L., Winocur, G., De Ruiter, M.B. & Castel, H. 2019. Cancer-related cognitive impairment: an update on state of the art detection and management strategies in cancer survivors. *Ann Oncol*. 2019 Dec 1;30(12):1925-1940. doi: 10.1093/annonc/mdz410.

Liu, P., Guo, L., Yu, X., Liu, P., Yu, Y., Kong, X., Yu, X., Zephania, H.M., Liu, P. & Huang, Y. 2023. Identification of region-specific amino acid signatures for doxorubicin-induced chemo brain. *Amino Acids*. 2023 Mar;55(3):325-336.

Macmillan Cancer Support

<http://www.macmillan.org.uk/information-and-support/treating/chemotherapy/side-effects-of-chemotherapy/chemo-brain.html>

Mahmoud, A.M.A., Mantawy, E.M., Wahdan, S.A., Ammar, R.M. & El-Demerdash, E. 2023. Vildagliptin restores cognitive function and mitigates hippocampal neuronal apoptosis in cisplatin-induced chemo-brain: Imperative roles of AMPK/Akt/CREB/BDNF signaling cascades. *Biomed Pharmacother*. 2023 Mar;159:114238.

Mayo Clinic

<http://www.mayoclinic.org/diseases-conditions/chemo-brain/basics/definition/con-20033864>

<http://www.mayoclinic.org/diseases-conditions/chemo-brain/basics/symptoms/con-20033864>

MD Anderson Cancer Center

<http://www.mdanderson.org/patient-and-cancer-information/cancer-information/cancer-topics/dealing-with-cancer-treatment/chemobrain/index.html>

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

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Olson, B. & Marks, D.L. 2019. Pretreatment cancer-related cognitive impairment – mechanisms and outlook. *Cancers (Basel)*. 2019 May 16;11(5). pii: E687. doi: 10.3390/cancers11050687.

Pondugula, S.R., Majrashi, M., Almaghrabi, M., Ramesh, S., Abbott, K.L., Govindarajulu, M., Gill, K., Fahoury, E., Narayanan, N., Desai, D., Ren, J., Nadar, R., McElroy, T., Moore, T., Majeed, M., Kalyanam, N. & Dhanasekaran, M. 2021. Oroxylym Indicum ameliorates chemotherapy induced cognitive impairment. *PLoS One*. 2021 Jun 3;16(6):e0252522.

Regier, N.G., Naik, A.D., Mulligan, E.A., Nasreddine, Z.S., Driver, J.A., Sada, Y.H. & Moye, J. 2019. Cancer-related cognitive impairment and associated factors in a sample of older male oral-digestive cancer survivors. *sychooncology*. 2019 May 27. doi: 10.1002/pon.5131. [Epub ahead of print]

Salerno, E.A., Rowland, K., Kramer, A.F. & McAuley, E. 2019. Acute aerobic exercise effects on cognitive function in breast cancer survivors: a randomized crossover trial. *BMC Cancer*. 2019 Apr 3;19(1):371. doi: 10.1186/s12885-019-5589-1.

Science Daily

<http://www.sciencedaily.com/releases/2008/04/080422103947.htm>

Sordillo, P.P. & Sordillo, L.A. 2020. The mystery of chemotherapy brain: kynurenines, Tubulin and Biophoton release. *Anticancer Res*. 2020 Mar;40(3):1189-1200.

Srivastava, R.K. & Singh, P. 2020. Stem cell therapies as a therapeutic option to counter chemo brain: a negative effect of cancer treatment. *Regen Med*. 2020 Jun;15(6):1789-1800. doi: 10.2217/rme-2020-0060. Epub 2020 Aug 26.

Susan G Komen

<http://ww5.komen.org/BreastCancer/LongTermSideEffectsofChemotherapy.html>

Toh, Y.L., Sharig Maitaba, J., Bansal, S., Yeo, A., Shwe, M., Lau, A.J. & Chan, A. 2019. Prechemotherapy levels of plasma dehydroepiandrosterone and its sulphated form as predictors of cancer-related cognitive impairment in patients with breast cancer receiving chemotherapy. *Pharmacotherapy*. 2019 May;39(5):553-563. doi: 10.1002/phar.2259. Epub 2019 Apr 4.

Tyagi, K., Masoom, M., Majid, H., Garg, A., Bhurani, D., Agarwal, N.B. & Khan, M.A. 2022. Role of Cytokines in Chemotherapy Related Cognitive Impairment of Breast Cancer Patients: A Systematic Review. *Curr Rev Clin Exp Pharmacol*. 2022 Mar 4.

Vannorsdall, T.D. 2017. Cognitive changes related to cancer therapy. *Med Clin North Am*. 2017 Nov;101(6):1115-1134. doi: 10.1016/j.mcna.2017.06.006. Epub 2017 Aug 25.

Wikipedia

http://en.wikipedia.org/wiki/Post-chemotherapy_cognitive_impairment

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