Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

2-Deoxy-D-Glucose (2-DG)

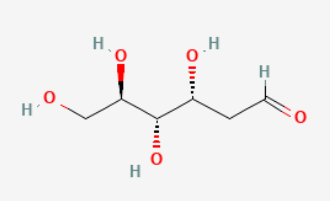
Evidence Summary

2-DG treatment may speed up recovery in patients with mild to serious COVID-19. There are several serious adverse events associated with 2-DG, including QTc prolongation and hyperglycemia.

Neuroprotective Benefit: No studies have tested the efficacy of 2-DG for dementia, age-related cognitive decline, or other neurological conditions.

Aging and related health concerns: 2-DG was approved in India for emergency use in COVID-19. Small open-label clinical studies suggest that 2-DG treatment may benefit some cancers, but larger rigorously-designed studies are needed.

Safety: Based on clinical trials in COVID-19 and cancer patients, adverse events with 2-DG are common and may be serious, including QTc prolongation and hyperglycemia. Other adverse events include palpitations, fatigue, dizziness, and diarrhea.

Availability: not approved for any indication in the US; approved for emergency adjunct therapy for COVID-19 in India; its radiolabeled form ([18F]fluoro-2-DG) is used as an imaging agent (FDG-PET)	**Dose**: not established; The doses tested in an open-label phase 2 trial in COVID-19 patients were 63, 90, and 126 mg/kg/day, orally, dissolved in water.	**Chemical formula:** $C_6H_{12}O_5$ **MW**: 164.16  Source: PubChem
Half-life: terminal half-life is 5-6 hours	**BBB**: penetrant	
Clinical trials: The largest clinical trial enrolled 110 patients with COVID-19.	**Observational studies**: none available	

What is it?

2-deoxy-D-glucose (2-DG) is glucose with the 2-hydroxyl group replaced by hydrogen, so it cannot undergo further glycolysis. 2-DG is predominantly used as an imaging agent in its radiolabeled form ([18F]fluoro-2-deoxy-D-glucose). By using positron emission tomography (PET), radiolabeled 2-DG can measure glucose metabolism (FDG-PET), which is altered in various age-related diseases such as cancer, cardiovascular disease, and neurodegenerative diseases including Alzheimer's disease.

As a glycolysis inhibitor, 2-DG is being studied as an anti-cancer and anti-viral agent (Singh et al., 2023). In 2021, 2-DG was approved for emergency use as an anti-COVID19 drug in India (Huang et al., 2022).

Neuroprotective Benefit: No studies have tested the efficacy of 2-DG for dementia, age-related cognitive decline, or other neurological conditions.

Types of evidence:

- 0 clinical trials
- 0 observational studies
- A few laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested whether 2-DG prevents dementia or improves cognitive function.

Human research to suggest benefits to patients with dementia:

No studies have tested whether 2-DG is beneficial for patients with dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

FDG-PET is used extensively as a marker of glucose metabolism in the brain in clinical research. There has been little research in the use of 2-DG as a therapeutic intervention for neuroprotection.

In rats under stress (immobilization stress and cold water swim stress), 2-DG treatment (0.4% in ad libitum food; 2 days on the diet and 1 day off) for 6 months significantly reduced resting blood pressure, attenuated blood pressure responses during stress, and accelerated recovery to baseline after stress (Wan et al., 2004). The 2-DG diet also improved glucose metabolism, as measured by decreased concentrations of blood glucose and insulin under non-stressful conditions, but glucose and insulin responses to stress were maintained. Thus, 2-DG treatment may reduce neuroendocrine responses to stressors. This study did not evaluate the effects of 2-DG treatment on cognitive functions.

APOE4 interactions: Unknown.

Aging and related health concerns: 2-DG was approved in India for emergency use in COVID-19. Small open-label clinical studies suggest that 2-DG treatment may benefit some cancers, but larger rigorously-designed studies are needed.

Types of evidence:

- 1 double-blind placebo-controlled clinical trial in genital herpes
- 4 open-label clinical trials
- Numerous laboratory studies
- Numerous review articles

Cancer: INCONCLUSIVE

Cancer cells utilize more energy than normal cells. In the 1920s, Otto Warburg discovered that cancer cells preferentially utilize glycolytic energy even in the presence of oxygen, referred to as aerobic glycolysis or the Warburg effect (Warburg, 1925). FDG-PET imaging also shows increased fluoro-deoxy-glucose uptake in tumors compared to normal tissue (Singh et al., 2023). Another rationale of using 2-DG in cancer is to target slow-growing cells found in hypoxic areas of solid tumors, which are not killed by chemotherapeutic agents (because they target rapidly dividing cells). Cancer cells in hypoxic conditions switch from aerobic to anaerobic metabolism and rely on glycolysis. When 2-DG is taken up by the cell, it competes with glucose and accumulates as 2-deoxy-D-glucose-6-phosphate, which competitively inhibits 2 enzymes needed for glycolysis (hexokinase and glucose-6-phosphate isomerase), leading to depletion of ATP, and induction of cell death. Thus inhibition of glycolysis with 2-DG is thought to kill these cancer cells.

In a phase I dose-escalation study of 34 patients with advanced solid tumors, 2-DG was administered orally once daily for 7 days every other week starting at a dose of 2 mg/kg and docetaxel was administered intravenously at 30 mg/m2 (1-hour i.v. infusion) for 3 of every 4 weeks (Raez et al., 2012). Following dose escalation, patients were treated with 2-DG for 21 days or everyday of each 4-week cycle for up to 12 cycles. The 2-DG dose deemed clinically tolerable was 63 mg/kg. One patient (3 %) had partial response, 11 patients (32 %) had stable disease, and 22 patients (66 %) had progressive disease. One patient with medullary breast cancer metastatic to lung and lymph nodes who had 8 prior systemic therapy regimens received 45 mg/kg 2-DG every other week and had a confirmed partial response with a duration of 65 days. Of the 11 patients with stable disease after 2 cycles (8 weeks) of therapy, 5 patients had stable disease for 2 more cycles (4 cycles), and 4 patients had stable disease for 4 more cycles (6 cycles). In 17 patients, tumor uptake of FDG-PET was evaluated and 5 had a decrease in uptake (range of 11-49% decrease). The patient with a partial response had a decrease in FDG-PET uptake of 11% after 1 week of 2-DG treatment alone that decreased further to -51% after weeks 3 and 4.

In a phase 1 open-label multiple dose study of 12 patients with advanced cancer (9 with advanced castrate-resistant prostate cancer, 1 with cervical cancer, 1 with nasopharyngeal cancer, and 1 with non-small cell lung cancer), the dose of 2-DG defined as recommended for a phase 2 study was 45 mg/kg, due to the dose-limiting toxicity of grade 3 asymptomatic QTc prolongation observed at the 60 mg/kg dose (Stein et al., 2010). 2-DG treatment was given orally on days 1-14 of a 21-day cycle in cohorts of three in a dose-escalating manner, started at 30 mg/kg, then 45 mg/kg, then 60 mg/kg. In 7 patients with prostate cancer who completed the study therapy, no declines in prostate-specific antigen were

seen. Three patients with castrate-resistant prostate cancer continued treatment beyond 3 cycles with radiographically stable disease (8, 12, and 21 cycles). Five of 8 patients assessed with FDG-PET demonstrated decreased FDG uptake by day 2 of 2-DG therapy, suggesting competition of 2-DG with FDG. Autophagy is a process in which cellular organelles and cytoplasm are targeted to lysosomes for degradation to supply an alternate source of energy during nutrient limitation. Five of 6 patients had a decrease in the autophagy substrate, p62, in peripheral blood mononuclear cells at 24 hours after 2-DG treatment, suggesting increased autophagy with the treatment.

In an open-label study of 12 patients with glioblastoma multiforme, 7 weekly fractions of (60)Co gamma-rays (5 Gy/fraction) were delivered to the tumor volume plus 3 cm margin, along with escalating doses of 2-DG (200, 250, and 300 mg/kg, orally) 30 minutes before irradiation (Singh et al., 2005). Four out of 10 patients who completed 2-DG treatment survived over 2 years (31-46 months), with a trend toward better survival with 300 mg/kg dose. This rate of survival was numerically higher than the average survival of glioblastoma multiforme patients treated with irradiation, where the 2-year survival at the time was under 10%. However, the study was small with an open-label design, so efficacy of 2-DG is inconclusive.

In human breast cancer cell lines, treatment with 2-DG results in cessation of cell growth in a dose-dependent manner (Aft et al., 2002). 2-DG treatment activates the apoptotic pathway in these cancer cells by inducing caspase 3 activity and cleavage of poly (ADP-ribose) polymerase. Breast cancer cells treated with 2-DG express higher levels of glucose transporter protein and have increased glucose uptake compared to non-treated breast cancer cells.

COVID-19: POTENTIAL BENEFIT

In an open-label randomized phase 2 trial of 110 patients with moderate to severe COVID-19, 2-DG treatment (63, 90, or 126 mg/kg/day, orally, dissolved in water) for up to 28 days (or until discharge) in addition to standard of care was compared with standard of care alone (Bhatt et al., 2022). Time to maintaining blood oxygen saturation (SpO2) ≥ 94% was 2.5 days (median) for patients who received 90 mg/kg/day of 2-DG, 3.0 days for those receiving 126 mg/kg/day of 2-DG, and 5.0 days for those in the other groups (standard of care and 63 mg/kg/day of 2-DG), with a statistically significant difference between the 90 mg/kg/day 2-DG and the standard of care alone group (p=0.0201). Also in the 90 mg/kg/day 2-DG-treated patients, times to discharge, to clinical recovery, and to normalization of vital signs were significantly shorter compared to the group receiving standard of care alone. The median time to clinical recovery, a composite endpoint, was 4.5 days, 3 days, and 4 days in the 2-DG 63 mg/kg/day, 90 mg/kg/day, and 126 mg/kg/day groups, respectively, and 5 days in the standard of care

alone groups, with a statistically significant difference between the 90 mg/kg/day 2-DG and the standard of care alone group (p=0.0003). The median time to normalization of vital signs was 5 days in the 2-DG 90 mg/kg/day group as compared to 8 days in the standard of care alone group (p=0.0026). Because this study employed an open-label design without a placebo control, placebo effects cannot be ruled out.

In COVID-19 patients, PET with radiolabeled 2-DG (FDG-PET) showed substantial accumulation in ground glass opacity lesions in the lungs (Liu et al., 2020), suggesting that 2-DG is preferentially taken up by SARS-CoV-2-infected areas of the lungs. Cell cultures infected with SARS-CoV-2 had increased metabolic demand and increased glucose influx, but 2-DG administration inhibited glycolysis, resulting in depletion of ATP required for SARS-CoV-2 multiplication and packaging (Bhatt et al., 2022). Virions from the 2-DG-treated cells also had reduced infective potential. Uninfected cells use both glycolysis and mitochondrial respiration to fulfill normal cellular energy demands and are less vulnerable to inhibition of glycolysis by 2-DG.

In May 2021, the Drugs Controller General of India approved the emergency use of 2-DG as an adjunct therapy in patients with mild to serious COVID-19 to speed up recovery and reduce the need for supplemental oxygen (Singh et al., 2023).

Infections: POTENTIAL BENEFIT
In a double-blind placebo-controlled study of 32 women with genital herpes infections, 2-DG treatment (gel of 0.19% 2-DG in micronazole nitrate, 2% crème) for 3 weeks cured 89% of cases, with 2 recurrences after 24 months (Blough and Giuntoli, 1979). In initial infections, discomfort cleared within 12 to 72 hours of therapy; 90% of the patients were asymptomatic and the lesions became negative for HSV within 4 days. In contrast, lesions became negative for HSV after 15 days for placebo-treated controls. In recurrences or secondary infections, 90% had notable improvements with no or less-frequent recurrences, fewer lesions, or shortened duration of symptoms. The duration of lesions following 2-DG therapy was approximately half of that observed in placebo-treated patients ($p<0.001$). 2-DG treatment also reduced virus shedding.

Cell culture studies have shown that 2-DG can interfere with multiplication of herpesvirus and viral-mediated functions such as fusion (Gallaher et al., 1973).

Lifespan: INCREASED IN NEMATODES
In nematodes (*C. elegans*) maintained on their usual food source (live *E. coli*), chronic 2-DG treatment extended maximum lifespan by 25% and mean lifespan by 17% (Schultz et al., 2007). Additionally, 2-DG

treatment limited to only the first 6 days of early adult life was sufficient to extend the nematodes' lifespan. Mean and maximum life span for control nematodes were 17.7 ± 0.4 and 27.9 ± 0.6 days, respectively. Mean and maximum life span for nematodes receiving 2-DG for life were 20.7 ± 0.5 and 35.0 ± 1.7 days, respectively. Mean and maximum life span for nematodes receiving 2-DG for 6 days were 20.6 ± 0.7 and 34.3 ± 1.3, respectively. Nematodes exposed to 2-DG had significantly lower body fat, suggesting increased β oxidation of fatty acids in states of glucose restriction. The mechanism by which 2-DG increased lifespan may be by promoting the formation of reactive oxygen species and inducing antioxidant defenses (catalase activity).

Oxidative stress: INCONCLUSIVE
In rats, 2-DG treatment (25 mg/kg/day, orally by gavage) for 12 weeks increased reactive oxygen species, which in turn increased antioxidant defenses (erythrocyte plasma membrane redox system, catalase and superoxide dismutase)(Saraswat et al., 2019). 2-DG treatment also decreased plasma sialic acid and advanced glycation end products. The authors proposed that low-dose 2-DG treatment could induce a mitohormetic response, resulting in enhanced defense mechanisms against stress.

Safety: Based on clinical trials in COVID-19 and cancer patients. adverse events with 2-DG are common and may be serious, including QTc prolongation and hyperglycemia. Other adverse events include palpitations, fatigue, dizziness, and diarrhea.

Types of evidence:

- 4 open-label clinical trials
- 1 review

In an open-label randomized phase 2 trial of 110 patients with moderate to severe COVID-19, 2-DG treatment (63, 90, or 126 mg/kg/day, orally, dissolved in water) for up to 28 days (or until discharge) was well tolerated and did not lead to altered rates of ICU admission or mortality compared to the group receiving standard of care alone (Bhatt et al., 2022). A total of 65 treatment-emergent adverse events were reported in 33 (30.3%) patients. Most of these (56 out of the 65 adverse events; 86%) were mild. Hyperglycemia was the most commonly reported adverse event overall, with 14 events occurring in 10 patients (9.2%): 6 patients in the standard of care group, 2 patients in the 2-DG 126 mg/kg/day group (9.5%), and 1 (4.5%) patient each in 2-DG 63 mg/kg/day group and 2-DG 90 mg/kg/day group. The incidence of hyperglycemia in 2-DG groups was not significantly higher than the group receiving

standard of care. There were no incidences of hypoglycemia. Other common adverse events were palpitations in 4 (3.7%) patients, dizziness in 4 (3.7%) patients, and diarrhea in 3 (2.8%) patients out of 109 patients, all of whom were in the 2-DG 63 mg/kg/day and 90 mg/kg/day groups with incidences ranging from 4.5 to 9.1%. One patient each in the 2-DG 90 mg/kg/day group and the standard of care group required ICU admission during the study. One mortality (4.5%) was reported in the 2-DG 90 mg/kg/day group, who died of acute respiratory distress syndrome, which was considered not related to the study intervention by the sponsor and investigator.

The greatest change in mean QTc intervals from baseline and the highest mean and median values were observed on Day 7 in the 2-DG 126 mg/kg/day group, with a mean increase of 23.8 ms from baseline, mean value of 446.7 ms, and median value of 444.0 ms (Bhatt et al., 2022).

In a phase I dose-escalation study of 34 patients with advanced solid tumors, 2-DG treatment (orally once daily for 7 days every other week starting at a dose of 2 mg/kg and increased up to 88 mg/kg) combined with docetaxel (administered intravenously at 30 mg/m2, 1-hour i.v. infusion for 3 of every 4 weeks) resulted in a higher incidence of QTc prolongation from 15% at baseline to 72% after 2-DG treatment, including 4 new grade 3 cases (Raez et al., 2012). Out of 33 patients receiving 63-88 mg/kg 2-DG, 5 patients (22%) had grade 1 QTc (Bazett's formula) prolongation, 8 patients (35%) had grade 2 QTc prolongation, and 5 patients (22%) had grade 3 QTc prolongation. One patient with grade 2 and 1 patient with grade 3 QTcB prolongation also developed T-wave inversion (often a sign of myocardial injury). The patient with grade 2 QTcB prolongation showed persistent T-wave inversion and died of cardiac arrest 17 days after the final dose of 2-DG (63 mg/kg, 21-day dosing). No ventricular arrhythmias, hypokalemia, grade 3 and 4 palpitations or chest pain were reported in any patient. Hyperkalemia occurred in 13 patients (38 %), including 1 patient with grade 3 hyperkalemia.

With regards other adverse events, the most common were fatigue, sweating, dizziness, and nausea (Raez et al., 2012). There were 2 patients with grade 3 fatigue. The clinically tolerable dose of 2-DG was 63 mg/kg. At this dose, one of 6 subjects had a dose-limiting toxicity of bleeding esophageal and gastric ulcers. This may be related to 2-DG-induced increase in gastric acid production. At doses of 63–88 mg/kg of 2-DG, plasma glucose concentrations increased significantly in the majority of patients after 2-DG levels reached maximum plasma concentrations at approximately 4 hours and then decreased to baseline by 12 or 24 hours. One of 5 patients at 2-DG 63 mg/kg dose and one of 6 patients at 2-DG 88 mg/kg dose had plasma glucose levels above 300 mg/dL although for less than 6 hours. The mean maximum plasma glucose concentration at 4 hours following 2-DG treatment was 274 mg/dl on day 1 of week 1, while it tended to decrease after multiple 2-DG doses (162 mg/dl on day 5 of week 1). The

transient hyperglycemia was not accompanied by elevations in hemoglobin A1c over time. At the 2-DG 88 mg/kg dose, all patients had symptoms of glucopenia (sweating, confusion, weakness, and dizziness) with elevated glucose levels as compared to baseline, indicating a significant block of glycolysis. One patient receiving continuous 2-DG dosing at 88 mg/kg had a dose-limiting toxicity of grade 3 QTc prolongation and no further patients were treated at this dose. One of 6 subjects treated at 2-DG 63 mg/kg dose had a dose-limiting toxicity of grade 3 QTc prolongation. Reasons for early discontinuation included disease progression (n=24), physician decision (n=4), adverse event (n=3; grade 3 QTc prolongation, sensory neuropathy, nausea/vomiting/dysphagia), and patient decision (n=3).

In a phase 1 open-label multiple dose study of 12 patients with advanced cancer (9 with advanced castrate-resistant prostate cancer, 1 with cervical cancer, 1 with nasopharyngeal cancer, and 1 with non-small cell lung cancer), 2-DG treatment (up to 60 mg/kg for 2 weeks of a 3-week cycle) resulted in a few grade 3 or 4 toxicities (Stein et al., 2010). The most common grade 1 and 2 toxicities were fatigue and dizziness. Grade 1/2 cardiac AV block was seen in 1 patient receiving 60 mg/kg 2-DG, grade 1/2 bradycardia was seen in 1 patient receiving 60 mg/kg 2-DG, and grade 1/2 QTc prolongation was seen in 1 patient each in the 30 mg/kg and 60 mg/kg 2-DG doses. Dose-limiting toxicity of grade 3 asymptomatic QTc prolongation was seen in 2 patients treated with 60 mg/kg 2-DG. Two additional patients were enrolled at the dose of 45 mg/kg 2-DG and none of the 5 patients had dose-limiting toxicity. Therefore, the recommended dose of 2-DG was 45 mg/kg.

In an open-label study of 12 patients with glioblastoma multiforme, 7 weekly fractions of (60)Co gamma-rays (5 Gy/fraction) delivered to the tumor along with escalating doses of 2-DG (200, 250, and 300 mg/kg, orally) 30 minutes before irradiation resulted in hypoglycemia in most patients (Singh et al., 2005). At the highest dose of 300 mg/kg 2-DG, 2 out of 6 patients were very restless and could not complete treatment. One of these patients had severe thirst, giddiness, and restlessness accompanied by nausea and excess vomiting. The other patient had excessive thirst and restlessness. While there were no life-threatening changes in vital parameters, including peripheral pulse rate, blood pressure, and body temperature, there was a decrease in body temperature in the range of 0.2 to 1.2°C indicating hypothermia in the first hour following 2-DG administration, which returned to normal by 2-3 hours. In most patients, a transient increase in blood pressure was noted after 2-DG treatment, which returned to the basal values by 2-3 hours. One patient receiving 200 mg/kg 2-DG experienced a fall in blood pressure to 80/60 mmHg. In one patient receiving 200 mg/kg 2-DG, laminar necrosis and ipsilateral ventricular dilation occurred during the 1-month and 8-month follow-up. Similar damage was not observed in the other 2 patients receiving this dose.

Drug interactions: Because 2-DG has been shown to cause QT prolongation, patients with cardiac conduction delay (QTc > 500 ms) or patients taking any medications known to prolong QT interval (e.g., hydroxychloroquine and azithromycin) should not take 2-DG.

Sources and dosing:

2-DG has been tested in early-stage clinical trials in cancer, COVID-19, and some infections. It is not approved for any indication in the US. In May 2021, the emergency use of 2-DG as an adjunct therapy in patients with mild to serious COVID-19 was approved in India (Singh et al., 2023). The doses tested in an open-label phase 2 trial in COVID-19 patients were 63, 90, or 126 mg/kg/day, orally, dissolved in water (Bhatt et al., 2022).

Research underway:

There are large numbers of clinical trials ongoing that are using 2-DG in the form of [18F]fluoro-2-deoxy-D-glucose as a diagnostic imaging agent (FDG-PET). With regards to 2-DG as an intervention, a randomized placebo-controlled double-blind phase 2 study is testing the efficacy and safety of 2-DG as a pre-exposure prophylaxis in a rhinovirus challenge model in healthy participants (NCT06375772). The primary outcome is the rate of rhinovirus-associated illness between 2-DG and placebo groups. The study is estimated to be completed in December 2024.

Search terms:

Pubmed, Google: 2-DG, 2-deoxy-D-glucose

Websites visited for 2-DG, 2-deoxy-D-glucose:

- Clinicaltrials.gov
- NIH RePORTER
- Examine.com (0)
- DrugAge (*C. elegans* studies)
- Geroprotectors (0)
- PubChem
- DrugBank.ca
- Labdoor.com (0)

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