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.

SXC-2023

Evidence Summary

May be beneficial in conditions where extracellular glutamate levels are too low, but activating system $x_c(-)$ could increase excitotoxicity and exacerbate damage in neurodegenerative conditions.

Neuroprotective Benefit: No studies have specifically tested the effects of SXC-2023 on neuroprotection. However, based on numerous preclinical studies, activating system $x_c(-)$ may exacerbate neurodegeneration.

Aging and related health concerns: No studies have tested SXC-2023 for age-related health conditions. Activation of system $x_c(-)$ may stimulate glioblastoma tumor growth/migration and worsen damage in cerebral ischemia.

Safety: Two phase I studies have shown that SXC-2023 is safe and well-tolerated, but no studies have tested its long-term safety yet. There are theoretical concerns for worsening the invasiveness of glioblastomas and the damage from cerebral ischemia.

Availability: under clinical development	**Dose**: effective dose not yet established; doses currently being tested in clinical trials range from 50-800 mg/day	**Chemical formula:** not reported **MW**: not reported
Half life: not reported	**BBB**: not reported	
Clinical trials: two phase I studies (n=40 and 48)	**Observational studies**: none	

What is it? SXC-2023 is a novel small molecule being developed by Prementis Pharmaceuticals for psychiatric disorders including trichotillomania (hair-pulling disorder) and obsessive-compulsive disorder (PrementisPharma.com). SXC-2023 activates system $x_c(-)$, which is a cystine/glutamate antiporter that exchanges extracellular cystine for intracellular glutamate. Intracellularly, cystine is reduced to cysteine, a building block of glutathione (GSH), which is an endogenous antioxidant (Massie et al., 2015). System $x_c(-)$ is expressed in the brain parenchyma, meninges, ependyma, astrocytes, and microglia, and in several brain regions, system $x_c(-)$ is the major source of extracellular glutamate. Therefore, system $x_c(-)$can affect excitatory neurotransmission, excitotoxicity, cognitive functions, and behavior by modulating the tone of extrasynaptic metabotropic or ionotropic glutamate receptors. SXC-2023 is designed to restore glutamatergic neurotransmission and imbalances in oxidative stress.

Neuroprotective Benefit: No studies have specifically tested the effects of SXC-2023 on neuroprotection. However, based on numerous preclinical studies, activating system $x_c(-)$ may exacerbate neurodegeneration.

Types of evidence:

- None specifically on SXC-2023
- Numerous laboratory studies examining the role of system $x_c(-)$ in neurological diseases

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
None available.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
No peer-reviewed research has reported neuroprotective benefits of SXC-2023 in animal models. However, based on the mechanism of action, activating system $x_c(-)$ may exacerbate neurodegeneration.

There is accumulating evidence from animal models of neurological diseases, which is in part supported by studies of human brain tissues, that xCT and system $x_c(-)$ are *upregulated* during neurodegeneration and contribute to damage in the brain (Massie et al., 2015). In theory, glutamate release via system $x_c(-)$ increases extrasynaptic glutamate, since glutamate reuptake via excitatory amino acid transporters (EAATs) is often perturbed in many neurodegenerative conditions (Sheldon and Robinson 2007). This increase could lead to the activation of extrasynaptic NMDA receptors, which can increase excitotoxicity.

However, it is worth noting that memantine, an FDA-approved drug for Alzheimer's disease, enhances system $x_c(-)$ activity in the rat brain (Okada et al., 2019). Memantine activates astroglial system $x_c(-)$, and glutamate released from system $x_c(-)$ to the extracellular space activates *inhibitory* metabotropic receptors (mGluR2/3) in the medial prefrontal cortex. The authors speculated that the combination of reduced NMDAR and activated system $x_c(-)$ contributes to the neuroprotective effects of memantine.

Cognitive functions: BOTH BENEFIT AND HARM ASSOCIATED WITH ACTIVATING SYSTEM $X_c(-)$
No studies have tested whether SXC-2023 specifically has cognitive benefits. Young mice (but not old mice) lacking a subunit of system $x_c(-)$ (xCT-/- mice) show impaired spatial working memory (De Bundel et al. 2011). However, overactivation of system $x_c(-)$ could also be deleterious to cognitive function by contributing to excitotoxic neuronal injury (Massie et al., 2015).

Alzheimer's disease: HARM ASSOCIATED WITH ACTIVATING SYSTEM $X_c(-)$
No studies have tested whether SXC-2023 is beneficial in Alzheimer's disease, but based on preclinical literature (described below), activating system $x_c(-)$ may result in exacerbation of neurodegeneration.

Increased expression of system xc(-) subunit, xCT, is seen in the cerebral cortex of an animal model of Alzheimer's (18-month old AβPP23 mice), where gliosis and Aβ plaques are prominent (Schallier et al. 2011). In wildtype mice, Aβ injection promoted microglial expression of xCT (Qin et al. 2006). The xCT gene is expressed not only in cultured microglia but also in reactive microglia within or surrounding amyloid plaques in transgenic mice expressing mutant human APP. In a neuron-microglia coculture, microglial system xc(-) was involved in the Aβ-induced death of cortical neurons (Qin et al. 2006).

In addition to APP and Aβ, several inflammatory factors including LPS, oxidative stress, and TNFα can also activate or increase the expression of macrophage/microglial system $x_c(-)$ (Piani and Fontana 1994; Sato et al. 1995; Mesci et al. 2015).

Parkinson's disease: MIXED/HARM ASSOCIATED WITH ACTIVATION OF SYSTEM $X_c(-)$.
No studies have tested whether SXC-2023 is beneficial in Parkinson's disease,

In xCT null mice injected with a neurotoxin (6-OHDA), dopamine neurons were significantly protected as compared to wildtype mice injected with 6-OHDA (Massie et al. 2011). The xCT null mice had 70% reduced extracellular glutamate levels compared to age-matched wild-type mice. However, in a different model of Parkinson's disease (MPTP), mice lacking xCT were equally susceptible to the neurotoxic effects of MPTP and motor impairment (Bentea et al. 2015b).

Multiple sclerosis (MS): HARM ASSOCIATED WITH ACTIVATION OF SYSTEM $X_c(-)$.
Increased expression of xCT, a subunit of system $x_c(-)$, is observed in leukocytes taken from human MS patients as well as in MS post-mortem optic nerve (Pampliega et al., 2011). Treatment with the nonspecific system $x_c(-)$ inhibitor sulfasalazine (SSZ), reduced the clinical severity in a mouse model of MS (EAE), which was associated with reductions in T cell infiltration, reactive gliosis, and myelin damage (Evonuk et al. 2015). Microglial system $x_c(-)$ up-regulation is thought to produce excitotoxic damage to myelin.

APOE4 interactions: Unknown.

Aging and related health concerns: No studies have tested SXC-2023 for age-related health conditions. Activation of system $x_c(-)$ may stimulate glioblastoma tumor growth/migration and worsen damage in cerebral ischemia.

Types of evidence:

- None specifically on SXC-2023
- Reviews on system $x_c(-)$

Glioblastoma: POTENTIAL HARM. No studies have tested SXC-2023 in glioblastoma patients or animal models. However, preclinical studies have suggested that activation of system $x_c(-)$ may promote glioblastoma tumor growth, glioblastoma cell migration, peritumoral neurotoxicity, epileptic seizures,

and chemotherapy resistance (Massie et al., 2015). Glioblastomas are brain tumors derived from glial cells and grow rapidly to invade healthy brain tissue. In glioblastomas, there is impaired glutamate uptake and increased system $x_c(-)$ activity (Ye et al., 1999). In patients with glioblastoma, high expression of xCT, the light chain of system $x_c(-)$, was significantly associated with shorter progression-free survival and shorter overall survival (Takeuchi et al., 2013). An inhibitor of system $x_c(-)$, sulfasalazine (SSZ), at a high dose (16 mg/day, i.p.) significantly inhibited the growth of glioblastoma cells implanted in the brain of mice (Chung et al., 2005).

Cerebral ischemia: POTENTIAL HARM. No studies have tested SXC-2023 in patients with cerebral ischemia or in animal models of cerebral ischemia, though based on its mechanism of action, it could potentially exacerbate damage.

In rat models of cerebral ischemia (transient middle cerebral artery occlusion), PET imaging showed a rapid increase in system $x_c(-)$ activity (Soria et al. 2014). Mice treated with a system $x_c(-)$/mGluR1 *antagonist* (LY367385) 3 hours after ischemia had reduced infarct volume (Li et al. 2013). And pharmacological inhibition of system $x_c(-)$ reduced cell death in slice cultures (Soria et al. 2014). In a mixed cortical cell culture system, enhanced astrocytic system $x_c(-)$ activity was a major contributor to excitotoxicity under conditions of energy deprivation (hypoxia or hypoglycemia), even though it was not harmful on its own (Fogal et al. 2007; Jackman et al. 2010).

Safety: Two phase I studies have shown that SXC-2023 is safe and well-tolerated, but no studies have tested its long-term safety yet. There are theoretical concerns for worsening the invasiveness of glioblastomas and the damage from cerebral ischemia.

Types of evidence:

- 2 phase I clinical trials

Two phase I clinical trials have been completed (NCT03301298; NCT03542435). The first one was a randomized, double-blind, placebo-controlled single ascending dose and food effect study to evaluate the safety and tolerability of SXC-2023 in 48 healthy volunteers (NCT03301298). The second study was randomized, double-blind, placebo-controlled multiple ascending dose study of SXC-2023 to evaluate safety and tolerability in 40 healthy adults (NCT03542435). Results of these 2 studies have not been published in peer-reviewed articles. But in a press release (PrementisPharma.com), SXC-2023 was reported to be "safe and well-tolerated over a wide dose range in healthy volunteers in both the single

ascending dose and multiple ascending dose studies, and demonstrated a very consistent pharmacokinetic profile". There were also no significant adverse events or treatment-related discontinuations in either study.

Drug interactions: Drug interactions for SXC-2023 have not been studied.

Sources and dosing: SXC-2023 is a novel small molecule currently under clinical development by Promentis Pharmaceuticals. The doses that were tested in phase I safety trials are not indicated in ClinicalTrials.gov. In the ongoing study for smokers who are abstaining from smoking (study described below), two doses of SXC-2023, 200 mg/day and 800 mg/day, are tested (NCT03887429). The other ongoing study is testing SXC-2023 in moderate-to-severe trichotillomania (hair-pulling disorder), and the doses being tested are 50 mg/day, 200 mg/day, and 800 mg/day (NCT03797521).

Research underway: There are two ongoing clinical trials testing SXC-2023 based on ClinicalTrials.gov. One is a randomized controlled crossover design phase 2 trial testing the safety and efficacy of SXC-2023 (200 mg/day, 800 mg/day, and placebo) in 24 non-treatment seeking smokers who are abstaining from smoking (NCT03887429). The treatment duration is 5 days with a 9-day washout period between treatments. Primary outcome measures include tolerability, adverse events, mood, abstinence-induced urges for cigarettes, and measures of impulsivity and inhibitory control. This trial is scheduled to be completed in June 2019. The other ongoing study is a double-blind placebo-controlled parallel-group trial testing the safety, tolerability, and activity of SXC-2023 in 120 patients with moderate-to-severe trichotillomania (hair-pulling disorder)(NCT03797521). Treatment duration is 6 weeks with 4 different arms: placebo, 50 mg/day, 200 mg/day, or 800 mg/day. Primary outcome measures are safety and tolerability including incidence of adverse events. Secondary outcomes include measures of hair-pulling frequency and severity. This study is scheduled to be completed in 2020.

Search terms:
Pubmed, Google:

- SXC-2023, SXC2023, Promentis

Websites visited for SXC-2023, SXC2023, Promentis:

- Clinicaltrials.gov
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)

- Drugs.com (0)
- WebMD.com (0)
- PubChem (0)
- DrugBank.ca (0)

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