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.

Sulfonylureas

Evidence Summary

May reduce risk of dementia in diabetic patients, but associated with increased risk of mortality relative to other anti-diabetics.

Neuroprotective Benefit: Limited clinical evidence suggests sulfonylurea use may reduce risk of dementia in patients with T2DM, and several preclinical animal studies suggest ways sulfonylureas may interfere with mechanisms of AD progression.

Aging and related health concerns: Large retrospective cohort studies and meta-analyses associate sulfonylurea use with decreased longevity or increased mortality in people with and without T2DM.

Safety: Short-term use of sulfonylureas is associated with hypoglycemia, nausea and weight gain. Chronic use appears to carry significant risks for both diabetic and non-diabetic patients.

What are they? Sulfonylureas belong to the class of "secretagogue" medications for type 2 diabetes (T2DM). They inhibit a potassium-ATP channel on beta-cells of the pancreas, stimulating the production and secretion of insulin. They include "first generation" drugs, "second generation" drugs like glibenclamide (Diabeta™, Glynase™, and Micronase™) which are more potent by weight than "first generation" sulfonylureas, and "third generation" drugs like glimepiride (Amaryl™). Third generation drugs are less likely than other sulfonylureas to cause the dangerous side effect of hypoglycemia (low blood sugar) and they can be used more safely in combination with other drugs for diabetes management (Davis et al, 2004). Most sulfonylureas carry some risk of hypoglycemia and weight gain. Interestingly, glimepiride is currently being studied as a potential treatment for both stroke-related edema and traumatic brain injury (see Future Research).

Neuroprotective Benefit: Limited clinical evidence suggests sulfonylurea use may reduce risk of dementia in patients with T2DM, and several preclinical animal studies suggest ways sulfonylureas may interfere with mechanisms of AD progression.

Types of evidence:

- No meta-analyses.
- One 2013 retrospective cohort study
- Limited rationale from preclinical studies

One large retrospective cohort study that followed ~800,000 initially dementia-free adults with T2DM over age 50 for 8 years found sulfonylurea use was associated with a 15% reduced risk of dementia, metformin use was associated with a 26% reduced risk, and use of the combination reduced dementia risk by 35% (Hsu et al, 2011). Additionally, several preclinical animal studies suggest mechanisms that sulfonylureas may improve Alzheimer's disease (AD) pathology. One study found that glibenclamide decreased hyperphosphorylated tau in the hippocampus and improved learning and memory in an induced rat model of AD (Baraka et al, 2010), while another suggests that glimepiride reduces Aβ production by suppressing β-secretase activity, and may act partially by stimulating PPAR-γ (Liu et al, 2013). One computational modeling study suggests that glibenclamide and glipizide may have inhibitory activity against mTOR (Khanfar et al, 2013), but this has not yet been shown experimentally. Preclinical evidence also suggests potential neuroprotective effects via anti-inflammatory and neurogenic activities (reviewed by Kurland et al, 2013).

There is no available data on whether one generation of sulfonylurea or another has more neuroprotective potential. It is important to note, though, that a side effect of sulfonylurea usage is

hypoglycemia and that chronic or recurrent hypoglycemia is a suspected risk factor for developing dementia. Glimepiride, a third generation sulfonylurea, appears to carry a lower risk of hypoglycemia that most of the second generation drugs (Basit et al, 2012).

APOE4 interactions: There is no available evidence for or against the idea that sulfonylureas may produce different effects in carriers of the *APOE4* allele. One preclinical study in cells and mice suggests that sulfonylureas do not appreciably interfere with cholesterol transport (Terao et al, 2011).

Interestingly, SNPs in the sulfonylurea receptor 2 (also known as *ABCC9*) were recently associated with an increased risk for hippocampal sclerosis, a disease often clinically-mistaken for Alzheimer's but pathologically unrelated (Nelson et al, 2014). Additionally, in those who died after age 85, sulfonylurea use was associated with a 2-2.5x increased risk of developing hippocampal sclerosis.

Aging and related health concerns: Large retrospective cohort studies and meta-analyses associate sulfonylurea use with decreased longevity or increased mortality in people with and without T2DM.

Types of evidence:

- 1 meta-analyses of RCTs
- 2 meta-analyses of 20-33 observational studies
- 2 large retrospective cohort studies not included in the above meta-analyses

Two recent meta-analyses of observational studies both conclude that sulfonylureas increase the risk of death in patients with T2DM compared to other diabetes medications. One analysis of 33 published studies (comprising over 3.1 million patients) reported an increased risk of cardiovascular-related death (Risk ratio (RR): 1.27; 95% CI: 1.18 to 1.34) and composite cardiovascular events (which include heart attack, stroke, and death) (RR: 1.10; 95% CI: 1.04 to 1.16) when compared to other diabetes medications (Phung et al, 2013). Another 2013 meta-analysis compiled 20 studies comprising over 500,000 patients found sulfonylurea use increased risk of both all-cause mortality (Odds ratio (OR): 1.92; 95% CI: 1.48 to 2.49) and cardiovascular-related mortality (OR: 2.72; 95% CI: 1.95 to 3.79) in patients with T2DM compared to other diabetes treatments (Forst et al, 2013). Both studies should be interpreted with caution because of high heterogeneity among included studies.

One recent meta-analysis of 62 RCTs reported an increased risk of mortality with sulfonylurea use (OR: 1.22; 95% CI: 1.01 to 1.49) by patients with T2DM (Monami et al, 2013). Again, while these results are concerning, they should be interpreted with caution due to differences in event reporting and trial duration among included studies. Additionally, two large retrospective cohort studies published in

2014 (not included in the above mentioned meta-analyses) comprising a combined ~150,000 patients both report increased all-cause mortality associated with sulfonylureas (Bannister et al, 2014; Morgan et al, 2014). One of these studies reported a 15% lower median survival time of non-diabetic patients taking sulfonylureas compared to non-diabetic patients taking metformin (Bannister et al, 2014). There is, as yet, no evidence to suggest differential associations of risk among the different types of sulfonylureas.

Safety: Short-term use of sulfonylureas is associated with hypoglycemia, nausea and weight gain. Chronic use appears to carry significant risks for both diabetic and non-diabetic patients.

All sulfonylureas are potentially teratogenic and should be avoided by women when pregnant. Medications like Aspirin and sulfa-based antibiotics are metabolized by the same liver enzyme used by sulfonylureas and may therefore prolong their effects in the body and should be used with caution when taking sulfonylurea drugs. Medications that lower glucose tolerance like oral contraceptives, corticosteroids and thyroid drugs should also be used with caution when taking sulfonylureas (Drugs.com).

Dosing and Sources: Most sulfonylureas are available by prescription as oral agents, though their half-lives vary greatly and require different doses and dosing schedules depending on the specific drugs.

Future research: Two on-going clinical trials are examining their potential to acutely treat both stroke-related edema (NCT 01794182) and traumatic brain injury (NCT 01454154).

PubMed Search terms: sulfonylurea (with and without filters for meta-analyses)

- + dementia
- + Alzheimer's
- + cognitive
- + longevity
- + mortality
- + comparative effectiveness
- + apolipoprotein
- + cardiovascular
- + traumatic brain

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