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GERIATRIC DISORDERS (W MCDONALD, SECTION EDITOR)

Natural Products and Supplements for Geriatric Depression and Cognitive Disorders: An Evaluation of the Research

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Abstract Numerous geriatric patients are using Complementary and Alternative Medicine (CAM) for late-life mood and cognitive disorders. Natural products and supplements are a common CAM intervention which have risks and benefits of which patients should be appropriately advised. The data for omega-3 fatty acids, ginkgo biloba, SAMe, St John's wort, B vitamins and vitamin D, huperzine, caprylidene, and coconut oil will be evaluated. Since the evidence basis for natural products and supplements is limited, especially for the geriatric population, studies involving the general adult population are included to infer effects in the aging population. Despite the data available, more rigorous studies with larger sample sizes over longer periods of time are still needed. Regardless of a physician's preference to recommend various natural supplements and products, a physician could protect their patients by having an understanding of the side effects and indications for various natural products.

Keywords Natural products · Supplements · Geriatric · Mood disorders · Cognition · Cognitive disorder · Dementia · Complementary and alternative medicine · Integrative medicine · Ginkgo biloba · SAMe · Omega-3 fatty acids · St. John's Wort · Huperzine · Vitamin D · Vitamin B · Caprylidene · Coconut oil · Folic acid · Pyridoxine · Cyanocobalamin

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Introduction

The aging baby-boom generation demonstrates a preference for choices regarding variety medical treatments and has a tendency toward utilizing natural products and supplements for various medical illnesses including mood and cognitive disorders [1]. There have been several reviews regarding the efficacy of Complementary and Alternative Medicine (CAM) for mood disorders in the general adult population [2], mood and cognitive disorders in the geriatric [1, 3] and cognitive disorders [4]. This article will review studies of natural products and supplements for geriatric depression and cognitive disorders in order to facilitate better patient education and safety. Unfortunately, as Qureshi and Al-Bedah (2013) state, CAM is an extremely popular but rarely studied treatment for mood disorders. Even less is known about how these interventions can be applied to older adults. Therefore a critical review of natural products and supplements in the general adult population must be utilized in order to infer effects for older adults.

Supplements and natural products are considered part of CAM. The National Center for Complementary and Alternative Medicine (NCCAM) describes CAM as various medical practices which fall outside of typical or allopathic medical treatment [5]. The focus of this article will be on natural products and supplements, which is included in one of several categories of CAM. Approximately 18 % of Americans had used a nonvitamin/ nonmineral natural product from the National Health Interview Survey (NHIS) in 2007 [6]. Physicians can better serve their patients by understanding the risk and benefits of various natural supplements and products.

Additionally, being open to discussing alternative agents can sometimes help to foster rapport in patients who have a preference for CAM. This review will focus on products, which have a stronger evidence basis including omega-3 fatty acids, ginkgo biloba, SAMe, St John's wort, vitamin B complex and vitamin D, superfine, and caprylidene.

Some of the products that will be discussed with fall under a category of medical foods, which includes agents which are regulated by the FDA with less stringency than medications, but more rigor than supplements. The Orphan Drug Act defines a medical food as "a food which is formulated to be consumed or administered entirely under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation" [7]. L-methyfolate, caprylidene and cerefolinNAC are three examples of medical foods used for the treatment of depression, Alzheimer's disease (AD), and the prevention of AD respectively. Other natural supplements, which will be reviewed, include omega-3 fatty acids, ginkgo biloba, SAMe, St John's wort, vitamin B complex, and vitamin D, huperzine, and coconut oil.

Omega 3 Fatty Acids

Omega-3 fatty acids (Ω3) are a common natural supplement utilized by Americans [6]. Sources of Ω3 come primarily from fish such as salmon but also are present in seeds and nuts, such as walnuts. Eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) are essential fatty acids, meaning the body does not have the enzymes to formulate them and therefore the body is dependent on the dietary consumption of these fatty acids [8]. Normal neuronal development in humans and rats depends on the concentration of Ω3 and deficiency of these fatty acids leads to delays in development [8, 9]. The popularity and evidence basis of Ω3 across the lifespan makes it an important supplement to review.

The data support an antidepressant effect of Ω3. Low levels of Ω3 are seen in individuals suffering from depression as well as in suicidal patients [10–12]. In the general adult population, **Ω3** fatty acids show an antidepressant effect when individuals are suffering from a clinical depressive episode as compared to having some depressive symptoms [13]. Another meta-analysis showed that Ω3 supplementations with ≥60 % of EPA had an antidepressant effect [14••]. Therefore for the general adult population, evidence supports a role for Ω3 supplementation in treating depression.

The data supporting Ω3 supplementation in geriatric depression is less extensive. There are no meta-analyses available for the geriatric population, however some randomized clinical trials (RCTs) examining the antidepressant effect of Ω3 exist.

Supplementation with Ω3 improved depression and quality of life in a small study of depressed females, age 66-95 years [15]. However, a subsample from a larger RCT of older adults, age 60-80 years old who had recently suffered a myocardial infarction showed an antidepressant effect with Ω3 supplementation [16]. The subsample consisted of those participants who were being prescribed an antidepressant. Therefore, there is some data to support the antidepressant effect of **Ω3** supplementation in older adults.

Studies have investigated the role of **Ω3** supplementation in bipolar disorder due to the role **Ω3** plays in cell membrane structure and the thought that deficiencies can lead to disruption of neuronal transmission and increased mood episodes [17]. The only evidence for bipolar disorder and Ω3 supplementation comes from a meta-analysis showing benefit for depressive episodes only and not manic or hypomanic episodes [18••]. At least 1000 mg per day, but no more than 3000 mg per day, of **Ω3** are recommended for bipolar depression [18••]. There are no studies including older adults with bipolar disorder which look at an antidepressant effect of **Ω3**. In conclusion, for the older adult who is suffering from a clinical depressive episode, supplementation with Ω3 may provide some antidepressant effect.

Ω3 supplementation may have cognitive benefits based on animal studies showing neuroprotection through anti-oxidant, anti-inflammatory, and anti-amyloid effects [19]. Epidemiological studies show fish consumption reduces the risk of AD [19]. There is a 47 % reduction in development of AD over 9 years with high plasma DHA compared to low DHA [20]. Additionally, the consumption of fish two to three times per week decreased the risk of dementia by half over 4 years in APOE-4 non-carriers [19, 21]. Therefore, dietary intake of Ω3 is related to a reduction in risk of developing AD.

However, the data regarding Ω3 supplementation and risk reduction in dementia are mixed. A meta-analysis showed Ω3 improved attention and processing speed in mild cognitive impairment (MCI) [22••]. Individuals who were cognitively normal or who had AD did not show any benefit with **Ω3** supplementation [22••]. The Cochrane database (2012) included three RCTs including approximately 4000 individuals being examined over a three year period concluded that Ω3 supplementation does not prevent cognitively normal individuals from developing AD [23••]. Therefore, Ω3 supplementation does not appear to treat dementia syndromes or prevent its occurrence however it does appear to slow the decline in MCI.

Some confounding variables might explain the mixed results among the studies [24]. In particular there appears to be an impact of APOE-4 allele carrier status, with APOE-4 non-carriers performing better with supplementation than APOE-4 carriers. Some studies have lost their blinding due to a common side effect of fishy aftertaste. There is a distinct difference between supplementation with Ω3 and the dietary consumption of Ω3. Therefore for the older adult wanting to prevent the

development of AD, one might suggest the importance of dietary consumption of Ω3 and for the older adult with MCI, one might suggest Ω3 supplementation to improve attention and memory.

St. John's Wort

St. John's wort (SJW) (hypericum perforatum) is a wildflower which has various standardized extracts available. The majority of data support the antidepressant effect of SJW. The only studies evaluating SJW and cognitive disorders come from animal models [25]. There have been many positive studies comparing SJW to placebo and standard antidepressants in general adult populations. A meta-analysis of 23 randomized trials with adults suffering from mild-to-moderate depression found an antidepressant effect with SJW [26]. Another recent meta-analysis showed similar efficacy and better tolerability of SJW when compared to standard antidepressants such as tricyclics (TCAs) and selective serotonin reuptake inhibitors (SSRIs) and superior efficacy when compared to placebo [27]. Most of the studies utilized SJW 300 mg three times daily although dosages ranged from 600-1800 mg daily [1]. Therefore, there is a strong evidence basis for SJW in treating the general adult population suffering from mild-to-moderate depression.

Despite the evidence supporting the antidepressant effect of SJW there have been multiple studies failing to show a clinical benefit [28–30]. When evaluating adults suffering from severe depression, SJW (900-1500 mg) did not show a significant difference when compared to placebo [31]. However, there were several factors which could have accounted for the negative findings, including a large placebo response and long duration of pretreatment symptoms (6 months-2 years) [31]. Therefore, the results are mixed with most evidence supporting the use of SJW in adults with mild-to-moderate, but not severe, depression.

There are only a few studies evaluating the efficacy of SJW in the geriatric population. The most convincing study is a six-week RCT in moderately depressed older adults (60-80 years old), which showed that SJW (800 mg extract LoHyp-57) had comparable efficacy to fluoxetine (20 mg) [32].

Additionally, there might be some benefit for SJW in atypical depression. An RCT of mixed-aged adults (18-70 years) with atypical depression showed benefit with SJW (600 mg extract LI-160) for atypical features of depression [33]. Therefore, the limited studies available do support the use of SJW for certain types of depression in the geriatric population.

A potential caution in using SJW in the geriatric population is the fact that SJW is associated with multiple drug-drug interactions [34, 35]. The major drug-drug interactions of SJW are related to its ability to induce cytochrome P-450 3A4 enzyme system that results in the increased metabolism of many medications including coumadin, methadone, alprazolam, clopidogrel, cyclosporine, and verapamil [25, 36]. Some older data report SJW acting as a monoamine oxidase inhibitor (MAOI) making its combination with standard antidepressants concerning for precipitating a serotonin syndrome, however newer data demonstrate SJW is an inhibitor of serotonin, norepinephrine, and dopamine reuptake [37••]. When used alone, SJW is usually well tolerated with the more common side effects including gastrointestinal symptoms, skin reactions and the possibility of photosensitization, headache, dizziness, fatigue, sedation, restlessness, anxiety, and dry mouth [37••]. One final potential side effect is for SJW to precipitate a manic episode [38••].

In summary the data would support the recommendation that for an older adult suffering from mild-to-moderate depression, who would rather not take prescription medication, one might suggest SJW. However, a thorough drug interaction search should be undertaken prior to being able to safely administer this medication.

SAMe

S-adenosyl-L-methionine (SAMe) is a naturally occurring compound in the body which is involved in the creation of the monoamine neurotransmitters and thereby is hypothesized to play a role in depression [39–41]. Previously, SAMe required parenteral administrations, however new oral formulations of SAMe have allowed ease in administration. There is evidence to support the use of SAMe in both mood and cognitive disorders.

Several studies support an antidepressant effect of SAMe. Depressed patients show decreased levels of SAMe and levels tend to increase in response to treatment [42]. SAMe supplementation has shown an antidepressant effect when compared to placebo and equivalent efficacy when compared to traditional antidepressants such as TCAs [43]. This analysis included mostly parenteral formulations and when they were compared to oral formulations, parenteral SAMe showed a slight superiority. Therefore there is strong evidence to support the antidepressant effect of parenteral SAMe in the general adult population.

The data supporting oral formulations of SAMe is growing. A six week open trial of adults (mean age 48.4 years ± 13 years) with partial response to standard antidepressants showed oral SAMe as being a beneficial augmenting agent [44]. Additionally, the same investigators designed an RCT with and found SAMe was significantly more effective than placebo as an augmentation strategy for non-responders to traditional antidepressants [45]. Another study looking at older patients (55-76 years old) suffering from Parkinson's disease with comorbid depression benefited from supplementation with SAMe

[46]. The most beneficial dosages of SAMe were 800-1600 mg/day, however dosages varied from 400-3600 mg [46, 47].

Therefore, SAMe can provide clinical benefit for depression particularly as a parenteral formulations, The evidence also supports the efficacy of oral formulations, especially as an augmentation strategy.

There are minimal side effects to SAMe. In fact one study showed the only significant difference in side effects with placebo was a trend toward increased systolic blood pressure and weight gain [45] whereas another study showed some transient gastrointestinal distress [46]. There have been reports of increased anxiety, mania and hypomania in patients with bipolar disorder using SAMe [48]. There was one case study of a 61 year old female suffering from depression, with a family history of bipolar disorder, who took SAMe and attempted suicide by self-burning [49]. Since SAMe is a commonly sold supplement over the counter and does not require a prescription or medical supervision, patients with bipolar disorder could suffer serious consequences unless they are being adequately monitored and being treated with a mood stabilizer.

Therefore, SAMe can be beneficial for depression, however the data is lacking for the geriatric population. An ideal candidate for a trial of SAMe could include a mildly symptomatic patient who would not have serious effects if there were a delay in treatment or a person who has failed multiple trials of conventional antidepressants and or is unable to tolerate side effects [47].

The data evaluating the efficacy of SAMe in cognitive disorders is less extensive than the data in depression. SAMe is thought to have a beneficial effect in the symptoms of AD via glutathione S-transferase (GST) activity, which is reduced in AD [50]. Parenteral SAMe improved Mini Mental Status Examination (MMSE) scores in a small open label study of older adults (64-83 years old) with mildly impaired cognition [51•]. A more recent study showed SAMe improved recall in depressed participants of a mixed age population (18-80 years old). However the results were confounded with the potential benefit to cognition by the antidepressant effects of SAMe independent of a direct effect on cognition [52]. Therefore, there is insufficient data available to support a cognitive enhancing effect of SAMe.

Ginkgo Biloba

Ginkgo biloba originates from the Maidenhair tree. It comes in various extract formulations. Ginkgo biloba is a neuroprotective agent which inhibits platelet activation, relaxes endothelium, inhibits cholinergic receptors, increases choline uptake in the hippocampus, and has antioxidant effects [53].

The data regarding Ginkgo biloba in various cognitive disorders has provided mixed results. A well designed RCT, the Ginkgo evaluation of memory (GEM), studied 3072 participants over the age of 75 years old with either normal cognition or mild cognitive impairment and did not find a protective effect of ginkgo biloba in preventing the development of dementia [52]. Another well designed RCT, the GuidAge study, evaluated 2854 older adults (over 70 years old) with normal cognition at baseline and failed to show a protective effect of ginkgo biloba on the development of dementia over 4 years showed a significant effect at 5 years [54••]. It should be noted that the incidence of dementia in this study was low 1.2-1.4/100 making it more difficult to detect a statistical difference. In another study, gingko biloba (120 mg of twice daily) did not prevent the conversion of adults aged 72-96 years old to AD [55]. Lastly a 20-year long epidemiological study, the PAQUID study, showed some benefit for ginkgo biloba in preventing dementia [56, 57]. However, given the exploratory and retrospective nature of this study, the consumption of ginkgo biloba was self-reported leaving the dosage and duration of administration being uncontrolled. Overall, the strongest available evidence does not support gingko biloba in the prevention of dementia unless it is supplemented over an extensive duration of time.

There is more data to support gingko biloba in the treatment of dementia as opposed to prevention of dementia. Gingko biloba (240 mg extract EGb761) was effective in outpatients (50 years or older) with mild-to-moderate AD or vascular dementia (VaD) [58]. There are reports of Ginkgo biloba reducing depression and counteracting sexual side effects of antidepressants in individuals with dementia [59]. It must be emphasized that many of the therapeutic effects of ginkgo biloba are found in small studies generally lacking a placebo group. Ginkgo biloba has not been shown to prevent dementia but may have a minor impact on cognitive decline in those already afflicted with certain types of dementia.

The most concerning side effect of ginkgo biloba is an increased risk for bleeding [53]. However there was a brief RCT in males on a ginkgo biloba extract (EGb 761) which failed to show an effect on coagulation [60•]. Other side effects include nausea, vomiting, diarrhea, headaches, dizziness, palpitations, restlessness, weakness, and rash [53]. In those individuals who are suffering from dementia, ginkgo biloba may be a helpful alternative to standard cognitive enhancers.

Huperzine A

Huperzine A (Huperzia serrata) is a Chinese herb. It has anticholinesterase effects as well as antagonistic effects on the N-methyl-D-aspartate (NMDA) receptor, both of which are thought to have beneficial effects in AD.

The results from studies of huperzine A and memory are mixed. Most of the positive studies of huperzine A come from China. Recently an RCT of older adults (60-80 years old) with VaD showed huperzine A improved activities of daily living (ADLs) and cognitive tests (MMSE & clinical dementia rating) [61••, 62]. However, in the US, a larger clinical trial showed only a modest effect of high dosage huperzine A (400 μg twice daily) on cognition [63]. Huperzine A was well tolerated with the most common side effect being nausea. However since there are no available long term studies the potential for other adverse effects remain unknown. Therefore, huperzine A has a modest potential benefit for dementia with minimal known side effects.

Vitamin B

Studies show low serum levels of vitamin B12 (cyanoboalamin) and vitamin B9 (folic acid) are involved in the formation of monoamine neurotransmitters and low levels are also seen in depressive states [64]. There is an increased risk for depression in older adults when vitamin B is low and homocysteine is high [65, 66, 67••]. Nevertheless, research regarding supplementation of vitamins B12 and B9 in individuals with normal levels are mixed. There was no effect of vitamin B12 and B9 supplementation in older adults (60-74 years old), with mild depressive symptoms in a RCT [68]. However, a combination of vitamin B12, B9, and B6 (pyridoxine) supplementation prevented depression in adults (mean ages 45.8-76.6 years old) after a stroke [69]. L-methyfolate is a medical food consisting of vitamin B9 and has been shown to provide an antidepressant effect as an augmentation agent to antidepressant medications in the general adult populations [69–71]. The data is lacking regarding an antidepressant effect for supplementation of B vitamins in older adults without a vitamin deficiency. The most promising results of vitamin B in the treatment of depression come from the supplementation of L-methyfolate to standard antidepressants as an augmentation. L-methyfolate is generally well tolerated however the potential for induction of mania was seen in the study [69].

Normally vitamin B12 and folate levels are assessed when evaluating a cognitive disorder as such deficiencies contribute to reversible causes of dementia [72]. Episodic memory deficits, slowed perceptual speed, and decreased total brain volume were seen in older adults with markers of vitamin B12 deficiency such as high levels of methylmalonate and homocysteine [73]. Interestingly, data have related elevated homocysteine levels to amyloid and glutamate toxicity and cognitive decline in animal studies [74•]. Therefore there it would seem likely that vitamin B supplementation would benefit cognitive disorders irrespective of therapeutic levels.

The supplementation of vitamin B deficiencies are the standard of care, however supplementing those individuals without a dietary deficiency must also be evaluated. Older adults with normal vitamin B12 and B9 levels and mild-to-moderate AD [74•] or VaD [75•] did not improve with vitamin supplementation. However those individuals without cognitive impairment appear to show a response to vitamin B supplementation. Immediate and delayed recall improved in older adults, ages 60-74 years old, without dementia and normal vitamin B12 and B9 levels [76•]. Therefore there is some data to support supplementation of vitamins B12 and B9 in individuals prior to the development of dementia.

CerefolinNAC (2 grams vitamin B12, L-methyfolate 5.6 mg, N-acetylcysteine 600 mg) is a medical food approved for the treatment and prevention of certain vitamin deficiencies seen in dementia [37••]. The data supporting CerefolinNAC is limited to a one- year uncontrolled, open label study of individuals with early AD. It is well tolerated, however side effects can include diarrhea, polycythemia vera, itching, swelling, nausea, vomiting, headache, and nephrolithaiasis [37••].

The risk of vitamin B supplementation must be compared with the benefit. There was an increase in mortality in vitamin B6 (HR 1.09; ARI 3.5 %) and vitamin B9 (HR 1.15; ARI 5.9 %) in a large epidemiological study, the Iowa Women's Health Study [77]. Additionally, it should be noted that in men folate supplementation contributed to re-stenosis of coronary stenting but no increase in infarction or death [78]. These studies highlight the need to acknowledge that being natural is not always safer than "conventional" medicine.

Vitamin D

The antidepressant effects of vitamin D supplementation is supported by correlation studies showing an increased risk of suicide with vitamin D deficiency [79•]. However, the data looking at the role of vitamin D supplementation and depression is mixed. In a study of older females at risk for Seasonal Affective Disorder there was no improvement in mood with vitamin D (800 IU daily) supplementation [80]. Another RCT looking at elderly women suffering from depression showed no benefit from vitamin D supplementation (400 IU daily) [81, 82•]. However, it is likely that higher dosages of vitamin D supplementation are required for an antidepressant effect. In a RCT of mixed-aged individuals (21-70 years old) who had low levels of vitamin D, these individuals were more likely to have depression; and when these individuals with vitamin D deficiency received supplementation with 40,000 IU per week there was an improvement in their depressive symptoms [83]. Also it appears that more moderate levels of depression respond better to vitamin D supplementation in an RCT of mixed age participants (20-60 years old) [36].

Vitamin D is generally well tolerated however the potential side effects include hypercalcemia and gastrointestinal discomfort [83]. Additionally, there appears to an association with both high (>98 nmol/L) and low levels (<46 nmol/L) of vitamin D and increased mortality in older men [84]. Therefore, when treating an individual for vitamin D deficiency one might find an antidepressant effect however there is not convincing evidence to support supplementation in individuals with normal vitamin D levels or mild depression.

Caprylidene/Coconut Oil

A new medical food called caprylidene has been marked to treat AD. Caprylidene consists of medium chain triglycerides that functions to elevate ketone bodies inducing a state of mild ketogenesis without a ketogenic diet [35]. There is decreased cerebral metabolism of glucose in AD [4]. Ketone bodies have been found to protect neurons, in vitro, from the toxic effects of beta-amyloid which is prominent in AD [85••]. Furthermore, ketones are thought to be more easily utilized by the failing AD brain [86]. There have been multiple studies looking at various types of ketone bodies and cognitive impairment, however there is only one RCT studying caprylidene in AD [85••]. In the study 152 individuals suffering from mild-to-moderate AD were supplemented with caprylidene. After 45 days of caprylidene treatment there was a small benefit on Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores (1.9 point), however this benefit was lost after 90 days but maintained in a subsample of APOE-4 non-carriers [87].

There are minimal known side effects from caprylidene including diarrhea, flatulence, dyspepsia, dizziness, and headache. Therefore, there is some limited evidence to support the use of caprylidene in the short-term for AD. For the individual with mild-to-moderate AD who wishes to utilize alternative means and cannot tolerate standard cognitive enhances, one might suggest the use of caprylidene.

Due to the expense and requirement to have a prescription for caprylidene, some individuals have instead looked to coconut oil. Despite popular reports in the media regarding coconut oil and treatment of AD, the data are not available to support such use. The assumed clinical effect comes partly from the fact that caprylidene has some ingredients from coconut oil as well as the highly publicized Newport Story. In the Newport Story, a physician Dr. Mary Newport, had given her husband large amounts of coconut oil and saw a benefit [86]. In this case study, there were other interventions that were used with the coconut oil including exercise, which could have accounted for the improvement. The side effects from coconut oil include increased low density lipoprotein (LDL), triglycerides, hypocalcemia, insulin resistance, and carcinogenesis. Therefore, the use of coconut oil is not recommended for those suffering from AD due to a risk benefit ratio in which the potential benefit does not outweigh the risks of the intervention.

Conclusion

Late-life mood and cognitive disorders are among the most common reasons older adults use CAM. Despite the growing use of natural supplements and vitamins by the aging US population, there is a scarcity of well-designed studies. Of those studies which are available, often times there are inconsistent results which can occasionally be attributed to various formulations of active ingredients. For this reason utilization of extract form would be ideal to ensure consistency of treatment effects. Acknowledging the option of CAM therapies in mood and cognitive disorders can facilitate the delivery of patient-centered care, as many individuals prefer natural products over prescriptions. Physicians can also protect their patients from the adverse effects of certain supplements by having a command of the literature, advising of side effects and minimizing polypharmacy. In summary, certain natural products and supplements can have beneficial and harmful effects for patients and physicians can assist in enhancing the health of their patients by providing direction on balancing such risks and benefits.

Compliance with Ethics Guidelines

Conflict of Interest Taya Varteresian declares no conflict of interest.

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- • Of importance
- •• Of major importance

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