Antiaging Treatments Have Been Legally Prescribed for Approximately Thirty Years

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ABSTRACT: There is an interesting divergence between the achievements of geriatrics and gerontology. On the one hand, during the last 30 years physicians in many developed countries have successfully prescribed several medicines to cure various symptoms of senescence. On the other hand, the influence of such medicines on human life span practically has not been studied. The most common of the relevant medicines are nootropic piracetam, gamma-aminobutyric acid (GABA), selegiline, *Ginkgo biloba*, pentoxifylline, cerebrolysin, solcoseryl, ergoloid, vinpocetin, sertraline, and estrogens, among others. Available data from human clinical practices and experimental animal studies indicate that treatments with these drugs improve learning, memory, brain metabolism, and capacity. Some of these drugs increase tolerance to various stresses such as oxygen deficit and exercise, stimulate the regeneration of neurons in the old brain, and speed up the performance of mental and physical tasks. This means that modern medicine already has "antiaging" treatments at its disposal. However, the influence of such treatments on the mean and maximal life span of humans, and on the age trajectory of a human survival curve has been poorly studied. The increase in human life expectancy at birth in the second half of the last century was mostly caused by the better survival at the old and oldest old rather than at the young ages. In parallel, the consumption of brain protective and regenerative drugs has been expanding in the elderly population. We provide evidence in support of the idea that the consumption of medicines exerting antiaging properties may contribute to the increase in human longevity.

KEYWORDS: antiaging drugs; longevity; cognitive functioning

HIDDEN ANTIAGING INTERVENTIONS

The prescription and consumption of nootropic, brain protective, and regenerative drugs is increasing in the elderly population. During the last three decades, geriatricians in the developed countries have successfully used these drugs to cure

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various symptoms of senescence. The most common of relevant medicines are nootropic piracetam, gamma-aminobutyric acid (GABA), ergoloid, estrogens, pentoxifylline, vinpocetin, *Ginkgo biloba*, cerebrolysin, solcoseryl, semax, sertraline, aspirin, and selegiline. There is strong evidence from human clinical practice and experimental animal studies that some of the brain protective and regenerative drugs significantly improve learning, memory, brain metabolism, and capacity. They are shown to increase the tolerance to various stresses such as oxygen deficit and exercise. Several agents may even stimulate the regeneration of neurons in the old brain and speed up the performance of mental and physical tasks.[1–21] The latter is very important because the age-related decline in the rate of information processing is a key feature of mammalian aging, and a potential antiaging intervention, in principle, should aim to reverse this decline. Thus, the therapeutic effect of several modern medicines is, in fact, an antiaging one. Some of these drugs are officially prescribed medications both in the United States and Europe. Hydergine (ergoloid mesylates), Trental (pentoxifylline), and Zoloft (sertraline) are examples. Others (e.g., piracetam and vinpocetin) have a long history (of up to 30 years) of successful prescription in Europe for the treatment of age-associated cognitive impairment and brain restoration after serious damage (e.g., after a stroke). However, they are used only as dietary supplements or drug compounds in the United States.

BRAIN PROTECTIVE DRUGS AND OLD AGE SURVIVAL: IS THERE A CAUSAL ASSOCIATION?

Curiously, the achievements of practical geriatrics and experimental gerontology diverge. On the one hand, the modern medicine unwittingly offers therapies with physiological "antiaging" effects. On the other hand, the impact of such "antiaging" treatments on the healthy life span, the age trajectory of a survival curve, and the longevity of humans have been poorly studied. In the second half of the last century, human life expectancy at birth increased owing to the better survival of the old and the oldest old rather than the young ages. Similarly, the prevalence of severe cognitive impairment in the elderly has declined in the last two decades in some developed countries.[22] In parallel, the consumption of medicines exerting antiaging properties has increased in the elderly population. It may have been one of the factors that contributed to both the increase in survival and the decrease in disabilities at oldest old ages. Indirect indicators of such an influence may be found in human and animal studies.

GABA and Piracetam

GABA and its chemical relative piracetam (Nootropil) are probably today's most common nootropic agents. GABA is a natural neuromediator transmitting inhibitory signals between neurons. It is used to treat the age-related memory impairment and the consequences of brain ischemia in the elderly. It has recently been shown to improve the cortical function in senescent monkeys.[1] In numerous studies, piracetam significantly improved learning, the performance of perceptual-motor tasks, and mental alertness.[2–5] Piracetam has been shown to regenerate neurons and increase neuronal receptor density.[3,4] Three randomized, double-blind, placebo-controlled,

clinical trials and one large population-based survey measured the influence of piracetam on the activities of daily living (ADL) of 6,000 elderly demented patients in Italy, Austria, and Belgium as well as on the basic nursing and therapeutic costs. It was found that piracetam treatment significantly decreased dependency, compared with placebo.[5]

Gingko biloba

Another common drug with nootropic action is a plant extract, namely, *Ginkgo biloba* (Tanakan). It has been shown to enhance memory and the speed of information processing in elderly and middle-aged individuals.[6–9] It also improves spatial learning, reduces indices of oxidative stress in brain tissue, diminishes cumulative oxidative changes, and accelerates functional recovery from hemiplegia in aged rats.[10–12] In a recent case–control study, treatment with *Ginkgo biloba* reduced the risk of developing Alzheimer dementia in a cohort of 1,462 community-dwelling elderly women aged 76 years and older.[13]

Deprenyl

Some of the brain-protective drugs provide protection against the age-related depletion of the dopaminergic nervous system. Deprenyl (selegiline) is probably the best example. This selective inhibitor of MAO-B is commonly used in clinical practices to treat symptoms of Parkinson disease. In animal studies, Deprenyl substantially increased survival of rodents and dogs up to twofold.[14,15] Named as Anipryl, it has been recently approved by the FDA (1999) for the treatment of cognitive dysfunction syndrome in aging dogs. The effects of the long-term use of deprenyl in healthy aging individuals, however, have yet to be studied.

Trental

Most of the nootropic drugs also improve the blood circulation in the brain. Separate agents such as pentoxifylline (Trental) do it preferably. This leads to the regression of age-associated circulatory insufficiency. Trental has been shown to reduce symptoms of vascular dementia and improve cognitive function and psychointellectual performance in elderly patients.[16,17]

Hydergine

A popular adrenergic nootropic agent in the United States, Hydergine (ergoloid mesylates) has been used to treat the impairment of mental function in the elderly. It has a modest effect related to improved performance and reduced retardation. An advantage of this drug is that it is very well tolerated and can be used for long-term treatment.[18]

Estrogens

Although estrogens are not prescribed directly as an antiaging treatment, many studies suggest such an effect, particularly on cognitive functioning.[19,20] Conjugated estrogens were shown to promote neuronal survival as well as reverse skin aging in preclimacteric women. Ashcroft and colleagues (1999) have found that delays in

wound healing in the elderly can be significantly diminished by topical estrogen in both male and female patients.[21] Unlike many other drugs, there are plenty of studies demonstrating improved survival among the long-term female estrogen users (relative risk of death from all causes varies 0.5–0.6 in most cases).[23–26] The FDA is currently reviewing new information on the neuroprotective characteristics of estrogens and will determine whether labeling should be respectively updated.

Aspirin

The association of aspirin use with cognitive performance in middle-aged adults has been shown to be modest. However, in persons 75 years and older, the positive effect of aspirin on the memory retention is significant.[27] The daily intake of low-dose aspirin also significantly improved survival in a Finnish centenarian cohort with a parallel shift of the survival curve to the right.[28] Such a pattern of the survival improvement resembles what we have observed recently in the general population.

Vitamin E

There are several "questionable" substances approved as dietary supplements in both the United States and Europe. These show some "antiaging" effect; however, available data do not allow a definite conclusion. Vitamin E could be example. It has been shown in an EPES (Established Populations for Epidemiologic Studies of the Elderly) study of 11,178 persons aged 67 to 105 years that the use of vitamin E significantly reduces the risk of all-cause mortality (RR = 0.66) and particularly the risk of coronary disease mortality (RR = 0.53).[29] At the same time, other studies suggest that supplementary vitamin E may worsen acute infections in the elderly.[30] Vitamin E protects tissues from oxidative damage that accumulates with age. However, the excessive antioxidative action may weaken immunity because some immune cells need oxidative agents to fight infection. Thus, it seems that dose-dependent effects of the vitamin E should be seriously taken into account in future studies of this agent.

Our Research in Progress and Preliminary Results

We are currently analyzing information on regularly taken medicines in aged (65+) noninstitutional individuals from the NLTCS (National Long Term Care Survey) (the USA) and the LSADT (Longitudinal Study of Aging Danish Twins) (Denmark) longitudinal studies of human aging. We are interested in the long-term effects of individual exposure to these medicines on the indices of health, aging, longevity, and cognitive functioning. Our preliminary results indicate that drugs that improve survival at old ages may do so via increasing the rate of information processing in brain. For example, the regular use of vitamin A alone significantly decreased five-year risk of death at ages 65+ (RR = 0.7) in association with enhanced mental alertness in the NLTCS sample. The regular use of iron supplementary tabs showed *negative* effect also on both old age survival and cognitive functioning. It significantly increased the chances of death (RR = 1.3) along with a decline in the mental alertness. The regular intake of multivitamins did not show any profitable outcome for the elderly subjects in our study.

CONCLUDING REMARKS

Taken together, the data suggest that some of the brain protective and regenerative drugs may decelerate and even reverse aging-related changes in an old organism, particularly in the brain. There is limited evidence about their positive influence on human survival and risk of disabilities in the old. An important question arises about the contribution of these medicines to the contemporary increase in human longevity. Our study in progress aims to answer this question at least in part.

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