

“pro-youthful factors” in plasma from young mice and a clinical trial of plasma transfusion from young donors to individuals with Alzheimer’s disease (AD).<sup>1,3</sup>

An additional hypothesis is proposed to explain this effect: that young plasma reverses age-related memory impairment by enhancing the peripheral amyloid sink and hence decreasing cerebral amyloid beta (A $\beta$ ).<sup>4</sup>

Accumulation of A $\beta$  in the brain is the pathological and molecular hallmark of AD, the most common dementia in elderly adults. Age-related increases in brain A $\beta$  impair memory by inactivating molecular promoters of memory such as cyclic adenosine monophosphate response element binding protein (CREB) and suppressing synaptic plasticity and neurogenesis.<sup>5</sup> In addition to deposition in the brain, A $\beta$  circulates in plasma, cerebrospinal fluid (CSF), and brain interstitial fluid as soluble and insoluble oligomeric forms. There is an intricate interplay between the production of A $\beta$  in the brain and its passage into the peripheral circulation; A $\beta$  can cross the blood–brain barrier attached to some proteins, which carry it to the liver for clearance, a process known as the “peripheral amyloid sink.” In the peripheral circulation, the majority of A $\beta$  is bound to serum low density–related protein 1 (sLRP1), which sequesters 70% to 90% of plasma A $\beta$ , and apolipoprotein E (ApoE). Emerging evidence suggests that there is an imbalance between brain production of A $\beta$  and its crossing into the peripheral amyloid sink in individuals with AD.<sup>4</sup> sLRP1 levels and its capacity to bind A $\beta$  are low in individuals with AD.<sup>6</sup> Similarly, certain isoforms of the serum A $\beta$  transporter ApoE, such as E4, are associated with a greater risk of AD.<sup>7</sup> There is evidence that reducing levels of circulating A $\beta$  in the periphery, thereby augmenting the peripheral amyloid sink, leads to lower cerebral A $\beta$  burden by shifting A $\beta$  from the central nervous system to the blood. More recently, it was shown that exchanging blood from mice with AD with blood from normal wild-type mice resulted in reduction of cerebral A $\beta$  deposition and improved spatial memory performance.<sup>8</sup>

The rejuvenating effect of plasma from young mice in cognitively impaired old mice may be due, at least in part, to a reduction of cerebral A $\beta$  through enhancement of the peripheral amyloid sink. The level and amyloid-binding capacity of the major peripheral amyloid sink, sLRP1, decline with aging.<sup>6</sup> Hence, infusion of young plasma would replenish the sLRP1 in the blood, which could then efficiently shift cerebral A $\beta$  to blood, decreasing cerebral A $\beta$  burden. In future studies, it will be important to investigate whether reduction in the burden of cerebral A $\beta$  through augmentation of the peripheral amyloid sink mediates the rejuvenating effect of plasma from young individuals or mice on age-related cognitive impairment. If that is the case, it would suggest a therapeutic trial of plasma pheresis instead of plasma transfusion in individuals with AD, because pheresis might be more suitable for elderly individuals, who may have cardiovascular compromise.

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## ACCESS OF ELDERLY ADULTS TO POTENTIALLY INAPPROPRIATE MEDICATIONS IN THE BRAZILIAN HEALTH SYSTEM

*To the Editor:* In Brazil, the population aged 60 and older, which is considered elderly,<sup>1</sup> increased from 4.9% of the population in 1970 to approximately 10% in 2010.<sup>2</sup> In a study conducted in Brazil with community-dwelling elderly persons, 34.5% used at least one potentially inappropriate medication (PIM). The factors associated with use of PIMs were drug use by illiterate elderly adults, black race, daily use of four or more medications, use of prescription drugs, and acquisition of the drug through the Brazilian health system as opposed to acquisition in drugstores.<sup>1</sup>

Most of the elderly population in Brazil are poor and receive public health services and medications through the Unified Health System (SUS), which is often the only avail-

able option to them.<sup>3</sup> The SUS focuses its efforts along the following two major lines: the Family Health Programme, which provides primary health care to 5,295 counties, and secondary and tertiary healthcare services, which a network of public or subcontracted hospitals and medical centers across the country supply.<sup>2</sup> The Brazilian Health Ministry established the Family Health Programme in 1994, which plays a strategic role in public health policy. The Brazilian Elderly Health policy was approved in 1999, and since this time, the Family Health Programme has been a link between the elderly population and the healthcare system.<sup>3</sup>

The list of drugs available through the SUS in several states and municipalities matches the National List of Essential Medicines (RENAME). A lack of available medications in the SUS can interfere with the continuity of treatment and may also affect the average monthly income of elderly adults.<sup>4</sup>

An analysis of RENAME 2010 showed that 9% of the drugs in this national list could be considered PIMs according Beers criteria 2003.<sup>5</sup> The medications available for primary care treatment in Brazil were analyzed in the same study, and 19.7% were found to be potentially inappropriate.<sup>5</sup>

An assessment of generic drugs conducted in 2008, which also used the 2003 Beers criteria, showed that 20 (6.7%) of the 299 generic drugs that Brazilians used were PIMs.<sup>6</sup> In 2011, the medications that the Program Right Dose of São Paulo deemed inappropriate for elderly adults were examined, and the evidence that each drug was inappropriate were analyzed.<sup>7</sup> Right Dose is a state program that provides free drugs to the population of the state of São Paulo. The authors showed that 25.5% of analyzed drugs were inappropriate for use by elderly adults according to the 2003 Beers criteria.

RENAME 2013 was divided into components, although this is simply a list and not a set of standard treatment guidelines and does not contain information on safe medication use. The basic component includes medications administered for primary care, which seeks to address the most common health problems of the population. The specialized component contains medications for treating rare diseases or diseases with a low prevalence and high cost. The strategic component contains medications for the control of endemic diseases, such as tuberculosis. RENAME 2013 also includes a list of drugs restricted to hospitals.<sup>8</sup>

A preliminary analysis of RENAME 2013 showed that the proportion of PIMs used in primary care was 28.1% using the Beers 2012 criteria<sup>9</sup> and 27.1% applying the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP) criteria.<sup>10</sup> The lack of more-appropriate therapeutic alternatives, which administrative barriers outside of the realm of clinical variables influence, can in turn influence the prescription of PIMs for elderly adults in the SUS. The ratio of available drugs for dispensing with full public sector funding, which may require the health system to implement systematic activities to improve the management and monitoring of these drugs in the elderly population, influences prescribing habits.<sup>1</sup> Although the criteria of effectiveness, safety, and costs, regardless of the age of the population, govern the selec-

tion of drugs that compose the RENAME, a review of RENAME using the STOPP and Beers criteria, or the development of a national prescribing criteria to evaluate the appropriateness of drug treatment in elderly adults, could improve this population's use of appropriate medications. This is especially important considering the growing elderly population in Brazil.<sup>2</sup>

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