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RESEARCH ARTICLE

An Updated Prioritization of Geroscience-Guided FDA-Approved Drugs Repurposed to Target Aging

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ABSTRACT

The biological mechanisms of aging drive the development of chronic diseases such as cardiovascular disease, diabetes, dementia, and cancer that dominate our current medical system. Geroscience-guided approaches seek to mitigate these pathological consequences of aging by targeting the fundamental hallmarks of aging. Using modalities that modulate these aging mechanisms to reinforce longevity we can prevent the onset of these diseases as well as target many of them at once. In this way, geroscience-guided approaches hope to extend both lifespan and healthspan in the near future. This article builds upon a previous paper which proposed a standardized process for evaluating FDA-approved medications for their geroscience potential and prioritized them to reflect preclinical and clinical evidence. In this article, we provide an update of the previous list of candidate gerotherapeutics to reflect the new and rapidly evolving evidence. We include the geroscience-guided evidence for three new FDA-approved drugs which did not have strong arguments for inclusion before: bisphosphonates, GLP-1 receptor agonists, beta blockers. This updated prioritization should help guide the efforts and financial investments for translating geroscience and allow immediate progress involving such candidate gerotherapeutics, especially the top 4 drugs: SGLT2 inhibitors, metformin, bisphosphonates, and GLP-1 receptor agonists. Since all of these drugs have been approved for safety and used extensively, repurposing them as gerotherapeutics should be considered in older adults.

1 | Introduction

With the discovery and implementation of modalities such as sanitation, vaccines, and antibiotics to address infectious diseases—which used to be the number one cause of death a century ago—life expectancy has now increased approximately 60%.[1] With humans now living longer than ever before, the leading causes of death have shifted from acute infectious processes to chronic age-related processes, with heart disease and cancer being the top two causes of death in the US today.[2] A growing body of evidence suggests biological aging to be the major modifiable driver of these two age-related diseases and other conditions associated with aging.[3] The ability to target the biological mechanisms of aging could reshape modern medicine's approach to managing these diseases. Rather than focusing on mitigating the endgame of these diseases, a more preventative approach by slowing down the molecular causes of aging would supplement the few tactics physicians currently have at their disposal to slow down aging: exercise, nutrition, and sleep. This approach, which has biological underpinnings, would also prevent multiple age-related diseases at once.

Advances in geroscience are encouraging the research of gerotherapeutics, which are pharmacological interventions that directly or indirectly target the widely accepted hallmarks of aging and, therefore prevent the development of the pathological consequences of aging such as cardiovascular disease (CVD), cancer, diabetes, and dementia. The benefits that gerotherapeutics provide on the cellular level, namely promoting a more youthful phenotype, appear to also translate to the organ and systemic level.

Despite the clear evidence that aging is the major risk for age-related disease and the WHO formally recognizing aging as a disease in its latest International Classification of Diseases, regulatory bodies such as the FDA and EMA do not yet recognize aging as a disease. One reason is the lack of studies investigating gerotherapeutics ability to delay the onset and progression of multiple age-related conditions, an issue that the Targeting Aging with Metformin (TAME) trial hopes to address. Without aging being considered a disease, insurance companies will not pay for gerotherapeutics. This disincentivizes pharmaceutical companies from developing novel gerotherapeutics simply because there is no financial incentive. Therefore, in large and well-designed clinical trials, there is an urgent need to investigate whether a cluster of age-related diseases instead of aging itself can be significantly delayed by repurposing existing drugs already approved by regulatory bodies.

Developed in consultation with the FDA, TAME is a large, multicenter clinical trial that hopes to address the lack of studies investigating whether a cluster of age-related diseases can be prevented with a gerotherapeutic, in this trial, metformin.[4] Despite only being indicated in diabetes, a vast body of evidence has suggested metformin to have beneficial effects on multiple age-related conditions such as CVD, cancer, Alzheimer's disease, and mild cognitive impairment, as well as reduced mortality.[4-6] For example, the UK Prospective Diabetes Study 34, which randomized over 1,000 patients with diabetes to metformin or conventional therapy, found that the metformin arm was associated with a 36% risk reduction for all-cause mortality ([9-55%], p=0.011).[7] By replacing aging with a cluster of age-related diseases, TAME hopes to establish the precedent that aging is not only a disease but one that can be treated.

Despite the promise of metformin's longevity-promoting effect, there is a long list of other potential gerotherapeutics backed by scientific evidence. Like what TAME is doing with metformin, there is a need for large randomized clinical trials (RCTs) to investigate these potential gerotherapeutics. Therefore, having a robust and up-to-date list of gerotherapeutics prioritized by their preclinical and clinical evidence is crucial to help guide these efforts. Building upon a previous paper that suggested a system to score evidence and rank drugs, we provide an updated list that includes adding new drugs based on new evidence.[3] Recognizing the need to initiate these TAME-like studies soon, we limit our analyses to potential gerotherapeutics that are already FDA-approved for other clinical indications.

We identified FDA-approved drugs or classes of medications with acceptable safety profiles with at least one publication showing extension of lifespan in rodents. We used the same 12-point prioritization scale that assigns equal points for the preclinical and clinical evidence for each of these candidates as was used in the original paper. Separate from this prioritization of drugs, we include mortality benefits seen in COVID-19 from each drug listed, as the resiliency of the immune system is believed to be associated with biological hallmarks of aging.[8] As the field of geroscience quickly advances, it will be crucial to maintain an up-to-date prioritization of gerotherapeutics designed to assess the likelihood of success in future large-scale multicenter clinical studies.

2 | Methods

Based upon new drugs included in DrugAge, a database for drugs that extend animal lifespan, evidence from a review of the literature, and discussions with experts in the field, we identified three new drug classes with acceptable safety profiles to be included in this update: GLP-1 receptor agonists (GLP1 RA), beta-blockers, and bisphosphonates. As our prioritization only has FDA-approved drugs, nutraceuticals and supplements were excluded.

Our review of the preclinical and clinical evidence for each drug followed the same protocol outlined in the original paper.[3] Preclinical categories included rodent lifespan, rodent healthspan, and hallmarks of aging. Clinical categories included human mortality and healthspan. Our scoring for each category was also the same as the prior paper, allotting a maximum of 6 points for preclinical evidence and 6 points for clinical evidence for a maximum of 12 points total.

Preclinical points were allotted using the following: (i) rodent lifespan: 0 points for no effect on lifespan or no applicable studies, 1 point for lifespan tested outside ITP, 2 points assigned for a significant increase in lifespan within ITP; (ii) rodent healthspan: 0 points for no effect on healthspan parameters or no applicable studies, 2 points for a positive effect on healthspan; (iii) hallmarks of aging: 0 points for no hallmarks, 1 point for one or two hallmarks, 2 points for three or more hallmarks.[9]

Clinical points were allotted using the following: (i) human mortality: drug needed to demonstrate that it reduced all-cause mortality or death from a disease which it was not intended to treat, with 0 points for no applicable studies or negative findings, 1 point assigned for observational studies, and 3 points assigned for RCTs; (ii) human healthspan: drug needed to demonstrate that it targeted at least one age-related disease/pathologic process which it was not intended to treat, with 0 points for no applicable studies or negative findings, 1 point assigned for observational studies, and 3 points for interventional RCTs. In addition, drugs with evidence supporting improved mortality from COVID-19 were distinguished with an asterisk in Table 1.

3 | Results

We prioritized a total of 12 drugs/drug classes as shown in Table 1. Since the original paper, 3 new drugs have been added and 3 old drugs have changed scores. Out of the new drugs, bisphosphonates received the highest score (11) followed by GLP1 RAs (10) and beta blockers (7). Regarding the old drugs that changed scores due to new evidence, D+Q and aspirin gained 2 and 1 point(s), respectively, in the area of human healthspan, while NAC gained 1 point in the area of hallmarks of aging. Given the ample preclinical and clinical evidence as well as testing in ITP, SGLT2 inhibitors (SGLT2i) remained at the top of the list with a perfect score of 12.

Gerotherapeutic	Hallmarks of aging	Preclinical healthspan	Preclinical lifespan	Human healthspan	Human mortality	Score (out of 12)
SGLT2 inhibitors	2	2	2	3	3	12
Metformin	2	2	1	3	3	11*
Bisphosphonates	2	2	1	3	3	11
GLP1 receptor agonists	2	2	0	3	3	10*
Acarbose	2	2	2	3	0	9*
Rapamycin	2	2	2	3	0	9
Methylene blue	2	2	2	3	0	9
ACE inhibitors/ARBs	2	2	1	3	0	8
Dasatinib + (quercetin)	2	2	1	3	0	8
Aspirin	2	2	2	1	0	7
Beta blockers	1	2	1	0	3	7
N-acetyl cysteine	2	2	1	0	0	5*

Table 1 Ranking of FDA-approved drugs as potential gerotherapeutics based on scoring (out of 12) for preclinical and clinical evidence. Evidence suggesting COVID-19 mortality benefit is delineated by an asterisk in the total score column.

Bisphosphonates

Existing evidence demonstrates that bisphosphonates target many of the biological hallmarks of aging including reducing oxidative stress, reducing DNA damage, promoting stem cell renewal, modulating epigenetics, reducing inflammation, and improving elements of metabolism (see Supplement 1).[10-16] In a mouse model of human premature aging, bisphosphonates (only studied in combination with a statin) have been

shown to alter the farnesylation and geranylgeranylation of prelamin A, a protein that is also altered during normal aging, preventing it's accumulation and improving aging-like phenotypes in addition to life expectancy.[17] In addition, the bisphosphonate zoledronate has recently found to extend both healthspan and lifespan of Drosophila by conferring resistance to oxidative stress and reducing DNA damage.[10] Interestingly, it was shown to manipulate the mTOR pathway and FOXO genes, both of which have been implicated as regulators of longevity.[18,19]

There is conflicting evidence regarding bisphosphonates and risk of all-cause mortality in humans. The first evidence came in 2007 when a RCT of annual zoledronic acid injections post-hip fracture were associated not only with decreased recurrent fractures but also with decreased all-cause mortality (see Supplement 2).[20] More trials followed, including a meta-analysis that investigated osteoporosis agents on all-cause mortality which showed a pooled analysis of all agents significantly reduced risk by 11%. However, analysis of each bisphosphonate individually (alendronate, risedronate, and zoledronic acid) did not produce significant results.[21] A subsequent larger meta-analysis in 2019 reported no significant change in all osteoporotic drug treatments as well as no change in bisphosphonates themselves.[22] However, trials of nitrogen-bisphosphonates such as zoledronic acid were associated with decreased mortality, albeit not significant (RR = 0.90 [0.81-1.00]), and there was evidence of high heterogeneity in this analysis (I^2 = 48.2%) as well as a higher proportion of non-bisphosphonate agents than compared to the 2010 meta-analysis limiting the accuracy of this analysis. Numerous observational studies have demonstrated clear mortality risk reduction in patients with vertebral or hip fractures.[23-25] Improved survival has also been found in non-fracture populations such as ICU patients.[26] A direct comparison between nitrogen (alendronate, risedronate) and non-nitrogen bisphosphonates (etidronate) found significantly better survival in nitrogen bisphosphonates.[27]

Bisphosphonates have been shown to have off-target healthspan benefits in human studies, supporting the belief that these drugs act beyond just the skeleton. They have been found to decrease the risk of CVD events including MI, stroke, and CVD-related deaths in patients with osteopenia, fractures, and rheumatoid arthritis.[28-31] Bisphosphonates have also been shown to decrease the risk of developing pneumonia as well as the mortality associated with pneumonia in patients with hip fracture.[32] A meta-analysis investigating cancer incidence found bisphosphonates to decrease the risk of colorectal, breast, and endometrial cancers but that non-nitrogen bisphosphonates increased the risk of liver and pancreatic cancers.[33]

GLP-1 receptor agonists

Caloric restriction (CR) in animals leads to a more significant increase in health- and lifespan than any drug, while obesity drives aging. The caloric-mimetic drug, GLP1 RA, was an obvious candidate to be added to our list. The evidence for GLP1 RAs targeting the hallmarks of aging has breadth across multiple hallmarks but needs more depth. These few studies have shown restoration of telomerase activity, increase in stem cell proliferation, increase in autophagy, and increase in mitochondrial activity (see Supplement 1).[34-37] Although no studies have investigated GLP1 RA's effect on rodent lifespan, several studies have reported positive effects on rodent healthspan. One study used rodent models of Alzheimer's, Parkinson's, and Wolfram disease to show that GLP1 RA's had a neuroprotective effect.[38,39] By boosting the activity of cardioprotective genes in mouse models of myocardial infarction (MI), GLP1 RAs have been associated with better cardiovascular (CV) outcomes as well as decreased blood pressure and more resilient endothelial function.[40,41]

Most of the human mortality research for GLP1 RAs has been in diabetic populations where overwhelming evidence has demonstrated a clear decrease in all-cause mortality (see Supplement 2).[42-45] A recent RCT looking instead at a population that had pre-existing CV disease and an elevated body mass index but without diabetes found that weekly semaglutide reduced the incidence of death from CV causes, nonfatal MI, or non-fatal stroke.[46] Several studies have examined GLP1 RAs effects on human healthspan within diabetic populations where they have been associated with a decreased risk of cognitive impairment and dementia, CV and renal outcomes, and colorectal cancer.[42,47-50] One recent trial in a population of patients with heart failure with preserved ejection fraction and obesity found that semaglutide significantly improved heart failure symptoms, exercise function, and weight loss compared to placebo.[51] Thus, the gerotherapeutics effects of GLP1 RAs, just like with SGLT2i and metformin, are effective not only in diabetics but in the non-diabetic populations, and they do not have the risk for hypoglycemia of hypoglycemic agents.

Beta blockers

There is little research available investigating beta blockers targeting of the hallmarks of aging. One study found that the beta blocker carvedilol

reduced oxidative stress-induced apoptosis in cardiomyocytes (see Supplement 1).[52] Another found that they modulate gene expression in a way that leads to increased ATP levels.[53] There are also limited studies investigating lifespan and healthspan in rodent models, although the beta blocker nebivolol is currently being tested in the ITP. A study investigating mice and Drosophila lifespan found that beta blockers increased the survival of both species, suggesting that these effects are phylogenetically conserved.[54] Another study found an effect of beta blockers in bone tissue, preventing against ovariectomy-induced bone loss in rats.[55]

Overwhelming evidence that beta blockers provide an all-cause mortality benefit in patients with heart failure earned it 3 points (see Supplement 2).[56-58] There are limited studies outside of this patient population, where it is suggested to offer mortality benefit through its dampening of the neurohormonal system. Meta-analyses have suggested decreased mortality in both COPD patients and dialysis patients but not in patients with stable angina.[59-61] One observational study found that beta blockers of any subclass were associated with increased mortality in diabetics; however, several limitations of the study include underpowering, the existence of possible confounders such as severity of heart failure and presence of atrial fibrillation, and inability to determine medication adherence.[62] Another question is whether the two predominant subclasses of beta blockers, beta-1 selective or non-selective, offer differing effects on mortality. One meta-analysis of interventional trials reported carvedilol, a non-selective beta-blocker, to decrease mortality significantly more than beta-1 selective beta blockers in patients with either heart failure or myocardial infarction.[63] However, the two beta blockers reported in DrugAge to have increased lifespan in mice were nebivolol and metoprolol, both beta-1 selective beta blockers.

There is insufficient evidence of beta blockers' effect on off-target age-related pathologies. A meta-analysis of observational studies investigating beta blockers reported no significant change in dementia risk when used alone without other anti-hypertensive medications.[64] In an observational study, beta blockers were associated with a decrease in cancer incidence; however, the same study conducted a meta-analysis of interventional trials which showed a decrease in cancer incidence, albeit this result was not statistically significant.[65]

Original drugs

New human healthspan evidence for D+Q includes a meta-analysis of RCTs that reported quercetin supplementation to decrease blood pressure in hypertensive and normotensive patients.[66] In addition, a recent RCT of elderly adults found that quercetin significantly improved their reaction time compared to placebo.[67] New human healthspan evidence for aspirin includes several meta-analyses of observational studies that report its use to be associated with decreased risks of breast cancer (RR = 0.92 [0.89-0.96]), ovarian cancer (13% risk reduction [6-20%]), and gastric cancer (HR = 0.72 [0.60-0.85]).[68-70] However, in two interventional trials investigating aspirin's effect on dementia incidence and cognitive decline, no significant results were found.[71,72] Importantly, both trials used anti-platelet level dosing (low dose), not anti-inflammatory (high dose) which many of the rodent studies used to demonstrate aspirin's effects on healthspan and lifespan. Gaining a point for demonstrating it targets several hallmarks of aging, NAC has been shown to decrease oxidative stress (only studied in conjunction with glycine), improve population doubling time of mesenchymal stem cells (only studied in conjunction with ascorbic acid), decrease the expression of senescence-associated genes, decrease mitochondrial dysfunction, and restore nutrient sensing.[73-75]

COVID-19 mortality

COVID-19 specific mortality data is overall fairly limited. Metformin has the best evidence of improved mortality outcomes with a meta-analysis of mixed studies demonstrating pre-admission use to be associated with decreased mortality compared to non-metformin users (RR = 0.60 [0.47-0.77]) and an interventional trial reporting a decreased composite of emergency department visits, hospitalizations, or mortality in metformin given after a COVID diagnosis (OR = 0.58 [0.35-0.94]).[76,77] A mostly observational meta-analysis of GLP1 RAs reported decreased mortality with pre-admission use (RR = 0.56 [0.42-0.73]).[76] Acarbose given after admission was associated with reduced mortality in an observational study of diabetics.[78] In a meta-analysis of mixed studies, NAC was shown to reduce mortality (RR = 0.65 [0.56-0.75]).[79] COVID-19 mortality data in SGLT2i users is inconclusive, with a RCT and a meta-analysis both reporting no significant results while another meta-analysis reported pre-admission use to be associated with decreased mortality in diabetics (OR 0.69 [0.56 - 0.87]).[76,80,81] No significant results were reported in studies of bisphosphonates, MB, ACEi/ARB, or aspirin; however, the meta-analysis of RCTs and aspirin only investigated anti-platelet level dosing, not anti-inflammatory.[82-84]

4 | Discussion

The geroscience hypothesis states that multiple

chronic age-related disorders such as CVD, cancer, diabetes, and dementia can be delayed or prevented through modalities that modulate the biology of aging.[85] The objective of geroscience is to translate the discoveries of basic research on the biology of aging to clinical care. Maintaining an up-to-date prioritization of drugs based upon basic science research as well as human research is necessary to help guide the development of future large-scale, multi-centered clinical trials such as TAME. We continue to restrict our list of candidate gerotherapeutics to FDA-approved drugs with acceptable safety profiles as we believe repurposing drugs already on the market will be faster and more cost effective than developing new compounds. We maintain the same scoring system used in the original paper, which gives equal weight to preclinical and clinical studies. In human studies, we include evidence for drugs that have either shown benefit in all-cause mortality or have a positive effect on off-target diseases or organ systems that the drug is not clinically indicated for. In doing so we hope to give candidate drugs a higher prioritization if they seem to be influencing age-related diseases beyond their clinical indication, further supporting the preclinical evidence that they target the biology of aging.

Thus, we provide a rigorous assessment of the literature concerning both preclinical and clinical status for several FDA-approved potential gerotherapeutics. As in the original paper, SGLT2i remained the only drug with a perfect score of 12/12, again beating out known potential gerotherapeutics such as metformin, rapamycin, and acarbose. The prioritization of bisphosphonates and GLP1 RAs in the top third of the list reveals that their preclinical and clinical evidence is significant with regards to potential gerotherapeutic effect. However, unlike metformin, bisphosphonates and especially GLP1 RAs remain quite expensive. For example, a year's supply of Ozempic (semaglutide), a popular GLP1 RA, costs roughly $10,000 without insurance. And without a diagnosis of T2D or obesity as an indication to prescribe the drug, insurance companies are less likely to provide coverage for its off-label use. However, as pharmaceutical companies scramble to get new GLP1 RAs federally approved, perhaps the rising supply will balance the cost, at least until aging is formally recognized as a disease.

We include COVID-19 mortality benefit evidence as the biological hallmarks of aging are theorized to apply on a systemic level, influencing the robustness of the immune system and the ability of our organs to recover from insults brought about by infection. The aging of the immune system, or immunosenescence, reduces a person's ability to fight infection.[86] We therefore theorize that gerotherapeutics with known capabilities of targeting biological aging mechanisms could also be used to enhance immunity by delaying immunosenescence. One-third of the drugs included in our prioritization have evidence of providing COVID-19 mortality benefit. The majority of the other drugs have not been studied in COVID-19 yet, although certain drugs such as rapamycin, which a recent meta-analysis of mice studies reported survival benefit from acute infection, have known immunomodulatory properties.[87] It will be interesting to see the results of these future studies as well as those that investigate the use of gerotherapeutics in other infectious diseases beyond COVID-19.

There are a number of nuances in geroscience that our study does not address including what dose and how often a drug should be taken, how different populations including age and sex contribute to effects, whether combinations of modalities are synergistic or antagonistic, and finally how different genotypes respond to gerotherapeutics. High doses of aspirin are required for its anti-inflammatory effect but this dosing would likely be too dangerous to use as a gerotherapeutic due to risk of bleeding which is even seen at low level anti-platelet dosing.[88] On the contrary, low doses of rapamycin rather than the typical high doses used clinically to achieve immunosuppression actually boosted the immune response to the influenza vaccine by 20% in an elderly population.[89] One small RCT that investigated the combination of metformin and aerobic exercise in healthy elderly found that metformin attenuated the increase in skeletal muscle mitochondrial respiration from exercise.[90] This could be due to metformin inhibiting mTOR, a protein kinase that when activated increases protein synthesis leading to muscle hypertrophy but decreases autophagy in addition to other functions. However, while gerotherapeutics such as metformin may limit muscle hypertrophy from exercise, they may also be altering age-associated deficits in muscle metabolism, allowing for better muscle function.[91] Despite debate over effects on muscle size, it is well known that inhibiting mTOR promotes health and longevity across various species.[92]

Another limitation of the human evidence in our study in drugs other than metformin, SGLT2i, and GLP1 RAs is that there is a general lack of research in populations outside of the one the drug is clinically indicated for. For example, bisphosphonate studies mostly investigated fracture patients while beta blockers mostly investigated

heart failure patients. Metformin, SGLT2i, and GLP1RAs, all considered drugs to treat T2D, have several robust studies conducted in non-diabetic populations. This highlights the need for more research, not only to demonstrate broad longevity benefits, but also to tease out the nuances that these geroscience-backed therapies almost certainly come with.

Looking forward, the geroscience research to come as well as the acceptance of aging as a modifiable disease in the public, clinician, and government domains will likely change the way medicine is approached in the near future. Rather than focusing on treating chronic diseases one-by-one as they emerge, geroscience-backed therapies will delay or prevent aging itself and therefore the development of many of these age-associated conditions. Apart from the benefits of increasing healthspan and lifespan, this leading form of preventative medicine has powerful political, economic, and societal gains as framed in The Longevity Dividend.[93] One paper that analyzed the economic value of increasing life expectancy by just one year was estimated to be worth $38 trillion annually.[94] Thus, society, in addition to the individual, stands to benefit tremendously from preventing age-related chronic diseases by targeting aging with gerotherapeutics, increasing the time we spend alive and healthy.

5 | Conclusion

We use a previously established scoring system to update a list of prioritized gerotherapeutics that are already FDA-approved based upon new evidence available. 3 new drugs including bisphosphonates, GLP1 RAs , and beta blockers were included. Bisphosphonates and GLP1 RAs scored considerably well given their ability to improve human healthspan and all-cause mortality, ranking third and fourth out of 12, respectively. Beta blockers, despite actively being studied in ITP, lack extensive preclinical evidence and have not yet shown significant benefit in human healthspan contributing to their low score. SGLT-2 inhibitors and metformin remain atop the list as most likely to succeed in future largescale clinical trials investigating biological age and age-related diseases. This prioritization of potential gerotherapeutics can help guide investigators in choosing which drugs to investigate in large-scale clinical trials.

Conflicts of Interest: None

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