Published in final edited form as:

Expert Opin Investig Drugs. 2017 June ; 26(6): 735–739. doi:10.1080/13543784.2017.1323868.

Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010–2015

Dev Mehta¹, Robert Jackson², Gaurav Paul³, Jiong Shi², and Marwan Sabbagh²

¹Lehigh Valley Health Network, Allentown, PA

²Alzheimer's and Memory Disorders Division, Barrow Neurological Institute, Phoenix AZ

³University of Arizona, Tucson, Arizona

Abstract

Introduction—There are dozens of drugs in development for AD with billions of dollars invested. Despite the massive investment in AD drugs and a burgeoning pipeline, there have been more setbacks and failures than treatment successes.

Areas Covered—The classes of drugs that have failed to date include the monoclonal antibodies, the gamma secretase inhibitors, dimebon, neurochemical enhances and one tau drug. Data for these compounds was sought through pubmed search and clinicaltrials.gov search.

Expert opinion—The obvious question to be posed is: Why are they failing? Is the treatment of symptomatic dementia too late? Are the therapeutic targets incorrect? Are the clinical methodologies imprecise, misleading or inaccurate? This review summarizes the drugs that have failed 2010–2015 and offers possible theories as to why they have failed.

Keywords

Alzheimer's; clinical trials; secretase inhibitors; monoclonal antibodies; dimebon; amyloid

1.0 Introduction

Alzheimer's Disease, which is a progressive neurodegenerative disorder that affects millions of people worldwide, is currently incurable. Only the symptoms are treatable, with much research being done in the form of clinical studies to try and develop disease modifying drugs that alter the progression. However almost all phase III clinical trials have failed to meet pre-specified endpoints in the past decade. Which begs the question, why are clinical trials failing in AD?

According to recent research into clinical trial (CT) methodologies, Alzheimer's disease (AD) drug developments and CTs remain vulnerable to lurking problems capable of compromising future research [1]. There are 4 drugs approved and currently used in symptomatic treatment for AD; donepezil 1997, rivastigmine 2000, galantamine 2001, and

memantine 2003. However, over 100 compounds tested as potential therapies were identified that were either abandoned in development or failed in CTs [2 of which are used to prevent progression of patients with Mild Cognitive Impairment (MCI) to AD].

There are many novel compounds that are in development for AD and MCI [3]. Concerns linger that methodological factors will interfere with the investigators being able to objectively assess the capabilities of the new AD drug candidates [2] [4]. Prior experiences with AD drug development, published reports on CT difficulties especially in neurology, psychiatry, and AD, as well as 40 AD drug developments randomly selected from AD drug candidates were considered to judge whether or not past problems in development of drugs for Alzheimer's can hurt research into the efficacy of drugs in CTs or about to enter CTs [1]. By taking a closer look at this, we can truly understand how AD drug development works to see where the underlying problem may be. Hence a variety of recently tested disease modifying drugs including monoclonal antibodies, gamma secretase inhibitors, tau aggregation inhibitors and symptomatic treatments such as neurochemical enhancers, and dimebon as well as and the clinical scoring tools used to evaluate their efficacy are reviewed. This review focuses on treatment failures between 2010 and 2015. Therefore drugs like aducanumab (BIIB037) and azeliragon (TTP488), which are still in development are not discussed.

2.0 Disease Modifying Failed Treatments 2010–2015

2.1 Monoclonal Antibodies

Anti-amyloid monoclonal antibodies (mABs) as a target for clearing amyloid have dominated the therapeutic landscape. Targeting amyloid is appealing as a therapeutic target as it is extra-neuronal and is associated with toxicity to the milieu. However, amyloid does not correlate with cognitive decline in the symptomatic phase of the dementia which could explain why the mABs have not succeeded to date.

3.1a Bapineuzumab—One of the first monoclonal antibodies to reach phase 3 trials that targets amyloid beta was Bapineuzumab [5] which targeted A β oligomers and plaque. In the phase 3 trials, CSF tau protein was reduced but no significant clinical benefit was seen in the cognitive or functional endpoints assessed. Limitations of this drug emerged when carriers of ApoE4 allele were more likely to develop vasogenic edema [12]. Because of a higher propensity of apo E 4 carriers to develop ARIA-E, the groups were split into separate studies with the apo E 4 carriers getting lower doses (0.5mg/kg) compared to the non E4 carriers (1–2mg/kg). Despite the incongruity of outcomes and the direction discordance of biomarker outcomes and clinical outcomes, there are possible explanations to consider. One key point to consider when assessing the phase III efficacy results is that the dose use in the phase III study (0.5mg/kg and 1mg/kg) is 10% of the original doses used in the phase I study. This reflects concerns about safety (vasogenic edema/ARIA-H). Thus, the dose might have been too low to demonstrate benefit. Another explanation is that the phase II study did not inform the phase III design fully. A third possibility is that bapineuzumab targeted the wrong isoform of Abeta.

2.1b Solanezumab—Solanezumab is another monoclonal antibody (mAB) that reached phase 3 trials [6]. Solanezumab targets monomeric Ab which suggests it targets amyloid pathology earlier in the disease process. Like the others anti-amyloid mABs, it did not meet the p primary or secondary endpoints in their phase IIB-IIIA study [13]. However, in a pre-specified post hoc evaluation of the data, the mild AD group was found to have 34% slowing in decline compared to placebo when Expedition 1 and Expedition 2 subjects were combined. This informed the design of the recently completed Expedition 3 study. Plasma levels of amyloid beta continued to rise from the time of first assessment to the last which suggests that Solanezumab transports the protein peripherally. This is consistent with engagement of soluble brain amyloid however PET scan shows that there is no effect on fibrillary amyloid. There was also no change in CSF levels of tau protein. The safety profile of this drug is excellent with very low incidence of vasogenic edema.

2.1c Crenezumab—Crenezumab has recently become relevant as it was selected as the drug for the Alzheimer's Prevention Initiative (API) trial [7] This trial follows families in Columbia who are asymptomatic that have the presenilin 1 (PSEN1) E280A mutation which predisposes carriers to early onset. This drug trial started in 2012 and will not finish until 2017 [16]. In Phase 2 trials, Crenezumab was found to have good penetration in the brain-blood barrier, good affinity for amyloid beta monomers, oligomers, and fibrils, and had not induced vasogenic edema seen in Bapineuzumab and Solanezumab. One of the primary endpoints besides prevention is to establish valid AD biomarkers so that future trials can be approved faster. The phase II results did not show a significant benefit in treatment compared to placebo but a post hoc analysis showed a benefit in mild AD subjects with an MMSE range of 22–26 [17,18]. A phase 3 trial is underway and currently enrolling patients.

2.1 d Gantenerumab—Gantenerumab failed to demonstrate significant clinical efficacy endpoint in phase 3 trials to date [8,9]. However, it was associated with reductions of brain amyloid beta standardized uptake value ratio (SUVR) in a dose dependent manner and CSF p-Tau and t-Tau which demonstrate brain amyloid clearance and an effect on downstream markers of neurodegeneration. It is hypothesized that increasing the dose may show a beneficial effect on patients [27]. A newly designed phase III RCT is underway at higher doses.

2.2 Gamma Secretase Inhibitors

2.2 a Avagacestat—It's suggested that inhibiting gamma secretase can decrease production of amyloid, including the highly amyloidogenic isoform AB42 [10]. In phase 2 trials, lower dose treated groups support for gamma secretase engagement as evidenced by analysis of CSF biomarkers. There was a dose dependent decline in in AB isoforms and volumetric MRI showed slightly more atrophy with treatment, although T-tau didn't show a significant decline. Clinically there was some improvement in patients however during a 12 week washout follow up, no clear indication of improvement or worsening was established. Larger doses were associated with increased side effects. In the prodromal cases, avagacestat increased the rate of skin cancers. Diarrhea, nausea and rash were more common in the treatment group. Because of the fairly narrow therapeutic window between efficacy and toxicity, avagacestat has not moved forward into phase III clinical trials.

2.2 b Semagacestat—This gamma secretase inhibitor reached phase 3 trials because in the phase I study, it showed clear dose dependent alterations of CSF biomarkers. The phase III was terminated by recommendation of the data and safety monitoring board [11]. Compared with placebo there was no improvement with cognitive function and patients receiving the higher dose had worsening of functional ability as well as more adverse side effects.

2.3 Tau

The tau protein has emerged as one of the appealing targets in dementia due AD. The tau hypothesis states that abnormal phosphorylation transforms normal tau into PHF-tau or neurofibrillary tangles. These then stabilize microtubule assembly which interferes with axonal transport which can lead to cell death [14]. There is extensive evidence that tangle accumulation correlates more reliably with clinical progression than amyloid [25]. Initial trials targeting this protein have been promising most significantly with TAI (tau aggregation inhibitors). Unfortunately, the results have not yet appeared in a peer reviewed journal. Most recently, the first tau-targeted therapy was unsuccessful after a fifteen month study studying mild-moderate dementia patient. Though unfortunate, there was a subset of patients (15%) who improved with this new drug, those not on any concomitant therapy. [15]

3.0 Symptomatic Failed Treatments 2010–2015

3.1 Neurochemical Enhancers

3.1 a Idalopiridine—Idalopiridine is a neurochemical enhancer that antagonizes 5-HT₆ receptors. Inhibiting 5HT₆ enhances acetylcholine release in the brain and is therefore pro-cholinergic. There are three trials that use this drug (STARSHINE, STARBRIGHT, and STARBEAM). STARBEAM and STARBRIGHT are currently still active and results will not be released until 2017. STARSHINE, though tolerated well, did not show improved performance on ADAS-cog beyond what was seen by donepezil.

3.1 b Encenicline—Encenicline works by increasing cholinergic response through direct agonism of the alpha 7 nicotinic acetylcholine receptors. The phase 3 trials has halted them due to GI toxicity by the drug trials were ultimately discontinued because the clinical trials on cognition in phase 3 failed to meet specified endpoints. In phase 2 trials, GI side effects were noted at the highest dose, 2mg. Phase 3 studies were performed at 2mg and 3mg. The patients receiving the higher dose had more severe symptoms.

3.2 Other

3.2 a Dimebon—Dimebon is an antihistamine that blocks H₁ histamine receptors. It also has a broad spectrum of effects including L-type and voltage-gated calcium channels, AMPA and NMDA glutamate receptors, α -adrenergic receptors and serotonergic receptors (24301650). It showed positive effects in Alzheimer's patients in small preclinical trials and one phase 2 trial in Russia (18640457). In 2010, two large phase 3 trials in the US, Europe, Australia and New Zealand failed to detect change in primary or secondary outcomes (23948924). [19]

4.0 Why are drugs failing? Expert Opinion

4.1 Targeting the Wrong Pathological substrates

In the last decade plus, the target almost commonly focused on for AD drug development has been amyloid beta plaques and their subsequent elimination. Bapinezumab, solanzumab, crenezumab, and gantenerumab all target different isoforms of Ab and different termini. The question is, if mABs are to work, should they target monomeric Ab, oligomeric, protofibrillar, or plaque. Should they target the N-terminus, C-terminus or mid domain.

4.2 Concerns with Drug Development

The current focus on AD and MCI by investigators is on disease modification rather than symptom remission. In AD drug development, the CT, originally designed for short-term evaluations of treatments, has not yet been successfully modified to give investigators confidence that disease modifying drug effects can be successfully treated [5] [6]. When long-term trials were done to try to detect disease modifying drug effects, the risk of losing subjects increased and there were other compromises to the integrity of the trial [7]. Furthermore, as a result of the outcomes of the long-term trials that were tried to make up for the shortcomings of the short-term trials, it has become widely accepted that trials that are able to test disease modifying drug effects will require larger numbers of subjects, greater numbers of clinical research sites, and longer double-blind evaluations. However, under these conditions, an increase in the loss of subjects, placebo responses, and life-events will undermine CTs easily.

Due to these confounding factors, the rate of AD drugs that are coming to market falls below the already low 7% rate for all central nervous system drugs []. On top of this, as many encounter as they attempt to evaluate development programs for drugs, many unsuccessful preclinical and clinical studies are not reported in literature and more importantly results are not released by sponsors. Investigators usually find problems of inaccuracy with CTs that are dependent on using clinical ratings as outcome measures [19]. Furthermore, similar measurement errors and a lack of specificity during diagnostic evaluations and qualifications of subjects for eligibility for clinical trials can lead to subjects being incapable of responding to treatment due to misdiagnosis, genetics, or specific pathology [20].

4.3 Problems with Raters

The Alzheimer's disease Assessment Scale – Cognitive (ADAS-Cog) is the most commonly used outcome instrument in CTs for treatments of dementia. However, variations in different forms, administration procedures and scoring rules, as well as rater turnover can decrease the reliability of the instrument. When 26 volunteer raters were surveyed, results showed that there were notable protocol variations in the forms used, as well as differences in scoring rules as mentioned above. Since change in this test over time is used to determine the effect of the treatment in CTs, it is better to have a standardized test and to address common problems to increase the instrument's reliability as well as its sensitivity to treatment effects [20].

Although the ADAS-Cog is the gold standard in clinical dementia trials, the administration procedures, work sheets, and scoring procedures of the ADAS-Cog were not clearly defined in the original article about the test [21] [22]. This problem is made even worse since responses to situations when working with a demented population are not very controlled and rarely addressed in training sessions at CT meetings. As a result, some raters may utilize their own judgements, leading to reduced inter-rater reliability. This problem was attempted to be fixed in 1998, when the Alzheimer's Disease Cooperative Study Group (ADCS) developed an ADAS-COG kit that revised the original manual and had more specific instructions, but even this was modified over time [23].

A study was done to see whether there is in fact variance in different forms of the ADAS-Cog test, and if so, find out what exactly was different. A 22 item survey was given to ADAS-Cog raters that were at a training meeting in 2007, on a voluntary basis. The survey covered many ADAS-Cog test topics such as test materials and administration procedures, and the participants were asked to "please answer the following questions based on the way(s) you have been instructed to give the ADAS-Cog or seen it given in the various clinical trials protocols you have worked with. Please circle *all* answers that you think are correct or *all* the ways you have seen it done." To determine the amount of variability, if a particular rater circled two or more answers for any questions that asked about specific procedures, then that meant that they were trained in more than one way to administer that particular item of the test. As a whole, this survey's purpose was to determine the percent of individual raters who had been trained to administer the ADAS-Cog differently depending on which clinical trial it was for (known as intra-rater difference), not necessarily to see whether different raters were just giving the test differently (inter-rater difference).

In terms of results of this study, the 26 raters that volunteered to take the survey varied in years of experience from 1–12 for giving the ADAS-Cog test (5.94 and the number of administrations that they had given varied from 40–1000). Additionally, the number of different protocols for the ADAS-Cog that were used differed between 3–20 with the majority being a combination of pharmaceutical industry sponsored and government sponsored. Many raters reported being trained differently on a certain item or on the scale as a whole, with 19.2% reporting that they were told to use different topics for the initial interview, and 73% reporting a different max amount of time allowed for stimulus exposure in the world list task. Most of these raters, around 65%, had given the ADAS-Cog for 7 or more CTs and had at least 5 years of experience with it.

This study shows, how there are in fact many inter-rater experience differences with administration of the ADAS-Cog. The exact impact of this on clinical trials is still unknown, although there is a good chance that it can affect the reliability of the data obtained from a CT. Also, using different methodologies in administering the ADAS-Cog could affect the validity of comparing outcomes amongst different protocols. Not only this; but the length of the clinical trial can play a big role any problems with the rater. The longer a clinical trial endures, the higher the chance that the rater that began the trial is not the same one that is completing the trial. Given that this study was smaller and only in North America, it is very possible that the results are not the most conclusive that they can be. Hence it would be helpful if a more uniform training method was established for all administrators of this test,

whether it be from a weekend training course to a more detailed video training session that discusses these inconsistencies in depth. From here, a larger multinational survey should be performed to confirm any results obtained in this study.

4.4 Problems with Methodologies

When looking at the many failures of the Alzheimer's treatment trials it is imperative to look at the different methodologies used to see if there are discrepancies from trial to trial. Tarenflurbil, an enantiomer of flurbiprofen, showed good results in phase 2 CT and demonstrated that there may be more efficacy in higher doses. The doses were described as safe and well tolerated in both AD and a prostate cancer trial. However, no dosing change was made from phase II to phase III trials revealed that this drug failure may be due to inadequate dosing. Metrifonate, an organophosphate acetylcholinesterase inhibitor, was shown to be toxic when given as a daily dose. Weekly dosing in two small clinical trials showed evidence supporting efficacy and safety. The drug did not receive FDA approval because of toxicity at higher doses. It raises the question of how the drug company advertised the medication, as a weekly or daily dosing. Phenserine, a non-competitive reversible acetylcholinesterase inhibitor, was advanced into a phase III CT without determining the optimal dose. In addition, it is unclear if the investigative sites were experienced with AD patients and rating scales. All of these individual variables combined could have led to the failure of the drug trial, rather than the drug itself.

4.5 Treatment may be too late

Similar to the previous trial of Bapineuzumab, it suggests that treatment should be started earlier. In addition, other avenues should be explored, not just targeting amyloid beta. The failure of clinical trials with bapineuzumab or gantenerumab can derive from the inability of these antibodies to target A β oligomers or from recruiting the wrong population (i.e. patients with advanced AD or early AD not adequately selected with biological markers such as amyloid deposition detectable by positron-emission tomography (PET)). There are also many that posit that some of the patients that are being selected are too advanced in terms of pathology within the disease process, and that therapy may be too little too late for these patients. The pathophysiological process of Alzheimer's is thought to begin decades before the diagnosis. The analyses of imaging, biomarker, and neuropsychological evidence have revealed that amyloid buildup followed up by other pathological changes have been in progress and peaked at the beginning of the mild cognitive impairment stage, when subtle clinical symptoms just become evident (21514248). The "preclinical AD" is conceptualized to capture this long silence period to facilitate longitudinal clinical research studies. Three prevention trials are currently underway (API, DIAN and A4) to address this crucial question. This will hopefully provide a clear answer on whether amyloid beta is the correct target.

Passive immunotherapy with aducanumab seems to represent the first example of a disease-modifying drug able to counteract the progression of this devastating disorder. These results have been obtained only in 2016, and not in 2010–2015. Nevertheless the recent positive results with aducanumab in prodromal and mild AD in a phase 1b trial demonstrate that "amyloid hypothesis" is still alive with the real hope to have new disease-modifying drugs

on the market, based on this hypothesis, in the near future and reinforce the timing of intervention with anti-amyloid treatments is a critical consideration.

Acknowledgments

Funding

This manuscript was supported by funding from the National Institute on Aging (P30 AG019610) and by the Barrow Neurological Institute.

Declaration of Interest

M. Sabbagh has received grants and research support from Astra Zeneca, Avid Pharmaceuticals, Axovant, Genentech Inc., Lilly Pharmaceuticals, Merck & Co, Pfizer, Roche Diagnostics corporation, vTv Therapeutics and Piramal Imaging. M Sabbagh has also acted as a consultant for Axovant, Biogen, Grifols, Humana, Lilly Pharmaceuticals, Sanofi, vTv Therapeutics and is a stock shareholder in Brian Health, Muses Labs and Versanum. J. Shi was the site principal investigator for Solanezumab and Dimebon trials.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Becker RE, Greig NH, Giacobini E. Why do so many drugs for Alzheimer's disease fail in development? Time for new methods and new practices? J Alzheimer's Dis. 2008; 15:303–25. [PubMed: 18953116]
2. Becker R, Greig NH. Alzheimer's disease drug development in 2008 and beyond: problems and opportunities. Curr Alzheimer Res. 5(2008):346–357. [PubMed: 18690832]
3. Giacobini E, Becker RE. One hundred years after the discovery of Alzheimer's disease. A turning point for therapy? J Alzheimers Dis. 12(2007):37–52.
4. Becker RE. Lessons from Darwin: 21st Century designs for clinical trials. Curr Alzheimer Res. 4(2007):458–467. [PubMed: 17908050]
- 5•. Vandenberghe R, Rinne J, Boada M. Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. Alzheimer's Research & Therapy. May 12.2016 Analysis of why bapi failed.
- 6••. Doody R, Thomas R, Farlow M. Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease. New England Journal of Medicine. Jan 23.2014 Primary report of solanezumab in two RCTs.
7. Miller G. Stopping Alzheimer's Before It Starts. Science. 2012 Aug.337:790–792. [PubMed: 22903991]
- 8•. Scheltens P, Nikolcheva T, Lasser R, et al. Biomarker Data from SCARLET ROAD: a Global Phase 3 Study of Gantenerumab in Patient's with Prodromal Alzheimer's Disease. Developing Topics: Clinical Trial Results. :331. Primary report of Gantenerumab RCT.
9. Lasser R, Ostrowitzki S, Scheltens P, et al. Efficacy and Safety of Gantenerumab in Prodromal Alzheimer's Disease: Results from SCARLET ROAD – A Global, Multicenter Trial. Developing Topics: Clinical Trial Results. :331–332.
- 10•. Coric V, Van Dyck C, Salloway S, et al. Safety and Tolerability of the gamma-Secretase Inhibitor Avagacestat in a Phase 2 Study of Mild to Moderate Alzheimer Disease. Arch Neurology. 2012; 69(11):1430–1440. Primary report of avagacestat RCT.
- 11••. Doody R, Raman R, Farlow M, et al. A Phase 3 Trial of Semagacestat for Treatment of Alzheimer's Disease. The New England Journal of Medicine. 2013; 369:341–350. Primary report of Gamma secretase inhibitor. [PubMed: 23883379]
12. Mohandas E, Rajmohan V, Raghunath B. Neurobiology of Alzheimer's disease. Indian Journal of Psychiatry. 2009 Jan-Mar;51(1):55–61. [PubMed: 19742193]

- 13••. Gauthier, et al. Lancet. 2016; 388:2873–84. Primary report of a clinical trial. [PubMed: 27863809]
14. Mullane K, Williams M. Alzheimer's therapeutics: Continued clinical failures question the validity of the amyloid hypothesis-but what lies beyond? Biochemical Pharmacology. 2013; 85:289–305. [PubMed: 23178653]
15. Miller G. Stopping Alzheimer's Before It Starts. Science. 2012 Aug;337:790–792. [PubMed: 22903991]
16. <https://clinicaltrials.gov/ct2/show/NCT01343966?term=ABBY&rank=1>
17. <https://clinicaltrials.gov/ct2/show/NCT01397578?term=MABT5102A&rank=3>
18. Bezprozvanny I. The Rise and fall of Dimebon. Drug News Perspect. 2010 Oct; 23(8):518–523. [PubMed: 21031168]
- 19••. Connor DJ, Sabbagh MN. Administration and scoring variance on the ADAS-Cog. J Alzheimers Dis. 2008; 15:461–464. An important report on why RCTs might be failing from a methodology standpoint. [PubMed: 18997299]
20. Davis KL, Thal LJ, Gamzu ER, Davis CS, Woolson RF, Gracon SI, Drachman DA, Schneider LS, Whitehouse PJ, Hoover TM. A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. The Tacrine Collaborative Study Group. N Engl J Med. 1992 Oct 29; 327(18):1253–9. [PubMed: 1406817]
21. Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry. 1984 Nov; 141(11):1356–64. [PubMed: 6496779]
22. Connor, DJ., Schafer, K. Administration Manual for the Alzheimer's Disease Assessment Scale. San Diego: Alzheimer's Disease Cooperative Study; 1998.
- 23••. Becker R, Greig N. Why So Few Drugs for Alzheimers Disease? Are Methods Failing Drugs. Current Alzheimer Research. 2010 Nov 1; 7(7):642–651. An important analysis on why methods are imprecise for AD assessments. [PubMed: 20704560]
24. Nelson P, Alafuzoff I, Bigio E, et al. Correlation of Alzheimer Disease Neuropathologic Changes with Cognitive Status: A Review of the Literature. J Neuropathol Exp Neurol. 2012 May; 71(5): 362–381.
25. Cummings J, et al. Alzheimers Dement. 2014; 10(4 suppl):P275. abstract O4-11-06.
26. Ostrowitzki S, Deptula D, Thurfjell L, Barkhof F, Bohrmann B, Brooks DJ, Klunk WE, Ashford E, Yoo K, Xu ZX, Loetscher H, Santarelli L. Mechanism of amyloid removal in patients with Alzheimer disease treated with gantenerumab. Arch Neurol. 2012 Feb; 69(2):198–207. [PubMed: 21987394]