ARTICLE

Risks and benefits of unapproved disease-modifying treatments for neurodegenerative disease

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Abstract

Objective

To determine whether patients randomized to unapproved, disease-modifying interventions in neurodegenerative disease trials have better outcomes than patients randomized to placebo by performing a systematic review and meta-analysis of risk and benefit experienced by patients in randomized placebo-controlled trials testing investigational treatments for Alzheimer disease, Parkinson disease, Huntington disease, or amyotrophic lateral sclerosis (ALS).

Methods

We searched MEDLINE, Embase, and ClinicalTrials.gov for results of randomized trials testing non–Food and Drug Administration–approved, putatively disease-modifying interventions from January 2005 to May 2018. Trial characteristics were double-extracted. Coprimary endpoints were the treatment advantage over placebo on efficacy (standardized mean difference in outcomes) and safety (risk ratios of serious adverse events and withdrawals due to adverse events), calculated with random effects meta-analyses. The study was registered on PROSPERO (CRD42018103798).

Results

We included 113 trials (n = 39,875 patients). There was no significant efficacy advantage associated with assignment to putatively disease-modifying interventions compared to placebo for Alzheimer disease (standardized mean difference [SMD] −0.03, 95% confidence interval [CI] −0.07 to 0.01), Parkinson disease (SMD −0.09, 95% CI −0.32 to 0.15), ALS (SMD 0.02, 95% CI −0.25 to 0.30), or Huntington disease (0.02, 95% CI −0.27 to 0.31). Patients with Alzheimer disease assigned to active treatment were at higher risk of experiencing serious adverse events (risk ratio [RR] 1.15, 95% CI 1.04–1.27) and withdrawals due to adverse events (RR 1.44, 95% CI 1.21–1.70).

Conclusions

Assignment to active treatment was not beneficial for any of the indications examined and may have been slightly disadvantageous for patients with Alzheimer disease. Our findings suggest that patients with neurodegenerative diseases are not, on the whole, harmed by assignment to placebo when participating in trials.

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Glossary

AD = Alzheimer disease; **ADAS-Cog** = Alzheimer's Disease Assessment Scale–Cognitive Subscale; **ALS** = amyotrophic lateral sclerosis; **ALSFRS** = ALS Functional Rating Scale; **CI** = confidence interval; **FDA** = Food and Drug Administration; **HD** = Huntington disease; **NNTH** = number needed to be treated for 1 additional patient to be harmed; **PD** = Parkinson disease; **RCT** = randomized placebo-controlled trial; **RR** = risk ratio; **SAE** = serious adverse events; **SMD** = standardized mean difference; **UHDRS** = Unified Huntington's Disease Rating Scale; **UPDRS** = Unified Parkinson's Disease Rating Scale; **WAE** = withdrawal due to adverse events.

Neurodegenerative diseases follow an inexorable course and markedly compromise quality of life and longevity. With few validated treatments that meaningfully affect progression, patients with neurodegenerative diseases may view clinical trials as opportunities to access potentially life-extending new treatments. In recent years, patient advocacy groups[1] and libertarian thinktanks[2] have also pressed for policies that would facilitate access to investigational therapies outside of trials.

Little is known about how such policies would affect patient outcomes; neither is much known about whether accessing unapproved treatments for neurodegenerative disease within trials confers advantages compared with receiving placebo. Because failure rates in neurologic drug development are so high[3,4] and no treatments for neurodegenerative diseases have demonstrated disease modification in large randomized trials,[5] unapproved treatments likely do not confer advantages beyond symptomatic relief.[6] Moreover, some putatively disease-modifying treatments have presented safety issues.[7,8] Nevertheless, small but statistically insignificant benefit associated with treatment assignment, when aggregated across trials, might add up to an overall advantage.

To address whether access to putatively disease-modifying treatments confers a clinical benefit to patients with neurodegenerative diseases, we performed a meta-analysis of randomized placebo-controlled trials (RCTs) testing unapproved interventions. We focused on Alzheimer disease (AD), Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington disease (HD).[9,10] To date, only 2 disease-modifying drugs have been approved by the US Food and Drug Administration (FDA) for these indications (one by European Medicines Agency), both for ALS and both showing a marginal advantage.[11,12] We hypothesized that patients assigned to placebo could have a small net clinical advantage over patients assigned to treatment due to side effects from unapproved interventions counterbalancing limited efficacy.

Methods

Data sources

Our sample of trials for this systematic review and meta-analysis was generated in 3 sequential steps. First, we identified a sample of drugs and biologics under development for each disease by querying ClinicalTrials.gov for all registered interventional trials of drugs or biologics involving each indication using Drug Trials Visualiser beta version 0.17.[13] We supplemented our list with drugs described on Alzforum,[14] the Michael J. Fox Foundation website,[15] the ALS Research Forum,[16] and the Huntington's Disease Society of America website.[17] Because dietary supplements, including vitamins and plant extracts, would be accessible outside trial participation, they were excluded from our sample. We defined supplements as any substance available without a prescription, either over the counter or through online order. Drugs and biologics were curated into their generic names, and synonyms were identified through searches of the disease-specific databases listed above.

In the second step, the drugs and biologics identified above were used as keywords in a search of MEDLINE and Embase for published RCTs testing each intervention in our sample in each of the 4 neurodegenerative diseases. The search strategy used for identifying RCTs is described elsewhere.[18] Publication database searches were supplemented with a search of ClinicalTrials.gov for trial results that had not been published elsewhere.

In the third step, trial reports were screened for eligibility using the following inclusion criteria: (1) published between January 1, 2005, and May 23, 2018; (2) original, full-length publications, abstracts, or results postings on ClinicalTrials.gov; (3) English language; (4) randomized and placebo-controlled trial; (5) single or double blinded; (6) enrollment of patients with a diagnosis of AD, PD, ALS, or HD; and (7) reported ADAS-Cog, UPDRS, ALSFRS, or UHDRS score as measures of efficacy. Trials were further screened on the basis of whether they tested unapproved agents for disease-modifying activity. Interventions were deemed unapproved if they had not been approved by the FDA for any indication before the study enrollment start date and thus would not be available to patients through off-label prescription. Interventions were deemed to be disease modifying if they met the following criteria: the aim of the trial was to treat the whole disease or symptoms that are prevalent and correlated with disease progression, and the intervention was not being tested as an adjunctive or add-on therapy. We defined add-on or adjunctive therapy as a therapy aimed at either enhancing or optimizing the effect of an existing therapy.[19] If a drug that had been tested as an adjunctive therapy was also tested in a separate monotherapy trial, this trial was still eligible for inclusion. Our screening process is illustrated in figure S1 (available from Figshare, https://doi.org/10.6084/m9.figshare.10052426.v2).

Data extraction

Trials were manually double-extracted with Numbat[20] to capture trial phase, study duration, patient enrollment, sponsor, and intervention. We extracted information on method of randomization, blinding, and patient withdrawals to calculate Jadad scores for risk of bias assessment.[21] We also extracted the methods of missing data imputation in the trials to supplement this assessment.

To assess benefit associated with treatment assignment, change from baseline to endpoint was extracted for treatment and placebo arms with the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog),[22] Unified Parkinson's Disease Rating Scale (UPDRS),[23] ALS Functional Rating Scale (ALSFRS),[24] or the Unified Huntington's Disease Rating Scale (UHDRS)–Total Motor Score[25] (the Total Motor Score subscale was chosen because several studies did not report the aggregated score or Total Functional Capacity subscale). We extracted the change in score from baseline to either the endpoint prespecified in the publication or the latest time point available if the final endpoint was not prespecified. For crossover, delayed start, and open-label extension trials, data were extracted from the last time point before switching or unblinding. For PD, because the UPDRS is composed of 4 subscales for which the total was not always available, we extracted in order of preference: the total UPDRS; the total of the Motor and Activities of Daily Living subscales (UPDRS II/III), or the Motor Subscale (UPDRS III). Furthermore, because UPDRS can be measured in the "on" or "off" state for patients experiencing motor fluctuations, we included only trials testing either previously untreated patients or treated patients experiencing motor fluctuations with scores reported in the "off" state. Trials of treated patients not yet experiencing motor fluctuations were excluded from the efficacy analysis.

To assess risk associated with treatment assignment, the reported proportions of patients experiencing serious adverse events (SAEs) and withdrawals due to adverse events (WAEs) were extracted for each arm. SAEs were defined as any adverse drug experience that is life-threatening or results in hospitalization, disability, or death.[26] SAEs of any cause were included because of the complexity of attributing causality in safety reporting.[27] If a trial reported a subset or multiple categories of SAEs and the total number of patients experiencing any SAE was not explicitly stated, we extracted the highest number without double-counting patients. WAEs were extracted as an additional measure of treatment risk. Total withdrawals used to calculate attrition rates included patients who withdrew either before or after receiving the study drug at any time before the prespecified final endpoint.

Missing data were sought from ClinicalTrials.gov or sponsor documents such as presentations or press releases. For publications in which efficacy data were presented graphically, we used graphical analysis software (ImageJ).[28] Investigators were contacted between August 27 and 29, 2018, if efficacy outcome data were incomplete.

Data synthesis

The primary analyses of safety and efficacy associated with treatment assignment were based on the subset of trials in our sample with >24 weeks of follow-up (long-duration trials). As a secondary analysis, we performed identical analyses in trials involving ≤24 weeks of follow-up (short-duration trials). Patient benefit was analyzed with a random-effects meta-analysis comparing the standardized mean difference (SMD)[29] in change from baseline between the treatment and placebo arms within each indication. All measures of variance were converted to SDs using the methods outlined in the Cochrane Handbook,[30] and multiple treatment arms in the same trial were pooled using inverse variance weighting.[31] Patient risk was analyzed with random-effects meta-analyses to calculate risk ratios (RRs) of SAEs and WAEs between the treatment and placebo arms. To facilitate interpretation, we also computed and present the risk difference and number needed to be treated for 1 additional patient to be harmed (NNTH).[32] A correction factor of 0.5 was added to SAE and WAE values for trials that reported zero event rates in both arms to allow these trials to contribute to the overall pooled effect size and confidence intervals (CIs).[33] Trials that did not report either SAEs or WAEs were not included in the respective analysis. Heterogeneity tests were performed with Higgins I^2.[34]

We performed subgroup analyses to probe whether safety and efficacy associated with assignment to experimental treatment differed between phase 2 and phase 3 trials. The p values for subgroup comparisons represent the between-subgroup heterogeneity statistic Q, based on a random-effects model. We also performed meta-regressions of efficacy, SAEs, and WAEs with the covariate of trial duration. To ensure that our definition of disease modification did not significantly affect our results, we reanalyzed our primary outcomes (table 1) comparing 2 modified definitions to our primary definition as sensitivity analyses. In the intent-based analysis, we included trials within our primary sample that expressed intent to develop a disease-modifying therapy. In the mechanism-based analysis, we included trials testing unapproved interventions that are not members of a drug class containing a previously approved symptomatic therapy (e.g., dopamine agonists for PD). In addition, we compared treatment advantage in subgroups stratified by the method used to combine dose arms (pooled vs high dose), methods of imputation used in the trials (mixed model repeated measures vs last observation carried forward vs observed cases), and attrition rates (<15% vs ≥15%).

We defined $p \leq 0.05$ as our threshold of statistical significance. Because of the exploratory nature of our analyses, we did not adjust for multiple outcomes and analyses.[35] All meta-analyses and statistical tests were performed with R version 3.4.2 with the meta package.[36] Analyses were prespecified before the outset of extraction, and the study was prospectively registered on PROSPERO (CRD42018103798).[37]

Table 1 Summary of primary outcome measures

	Efficacy	SAEs			WAEs		
	SMD	RR	RD	NNTH[a]	RR	RD	NNTH[a]
Alzheimer disease	−0.03 (−0.07 to 0.01)	1.15 (1.04–1.27)	0.03 (0.01–0.05)	33 (20–100)	1.44 (1.21–1.70)	0.03 (0.02–0.05)	33 (20–50)
Parkinson disease	−0.09 (−0.32 to 0.15)	1.32 (0.70–2.48)	0.03 (−0.03 to 0.08)	33 (NNTB 33 to ∞ to NNTH 12)	1.35 (0.86–2.11)	0.01 (−0.01 to 0.02)	100 (NNTB 100 to ∞ to NNTH 50)
ALS	0.02[b] (−0.25 to 0.30)	1.22 (0.82–1.80)	0.04 (0.00–0.09)	25 (11 to ∞)	0.88 (0.57–1.35)	−0.01 (−0.03–0.02)	−100 (NNTB 33 to ∞ to NNTH 50)
Huntington disease	0.02 (−0.27 to 0.31)	1.40 (0.50–3.89)	0.04 (−0.04 to 0.11)	25 (NNTB 25 to ∞ to NNTH 9)	1.18 (0.41–3.37)	0.02 (−0.05 to 0.09)	50 (NNTB 20 to ∞ to NNTH 11)

Abbreviations: ALS = amyotrophic lateral sclerosis; NNTB = number of patients needed to be treated for 1 additional patient to benefit; NNTH = number of patients needed to be treated for 1 additional patient to be harmed; RD = risk difference; RR = risk ratio; SAE = serious adverse event; SMD = standardized mean difference; WAE = withdrawals due to adverse events.
SMD < 0, RR < 1, and RD < 0 indicate treatment advantages. Efficacy and safety endpoints for trials in our primary analysis sample (long-duration trials with available data). The 95% confidence intervals are given when appropriate.
[a] NNTH calculated from rounded RD values.
[b] The sign of the efficacy mean for ALS was switched because a negative change on the ALS Functional Rating Scale corresponds to a decline, while negative changes on Alzheimer's Disease Assessment Scale–Cognitive Subscale, Unified Parkinson's Disease Rating Scale, and Unified Huntington's Disease Rating Scale correspond to improvements.

Ethics

Our study does not involve human participants and thus was not submitted for ethics review.

Data availability

Supplementary figures, tables, and references are available from FigShare (figures S1–S6, tables S1–S6, and e-references available at https://doi.org/10.6084/m9.figshare.10052426.v2). Raw data will be made available to investigators on request to the corresponding author.

Results

Trial characteristics

We identified 113 trials that met eligibility (figure 1): 69 AD trials; 20 PD trials; 16 ALS trials; and 8 HD trials. Of these, 52 were long-duration trials included in our primary efficacy analysis; an additional 10 trials reported safety but not efficacy endpoints and were included only in our primary safety analyses. Studies included in our primary safety analysis enrolled 31,029 patients, with 18,565 assigned to experimental treatment, and tested interventions consisting of 45% small-molecule drugs, 34% large-molecule drugs, and 21% biologics. With the exception of 1 trial, all trials scored ≥3 for quality with the Jadad scale (figure S2 available from Figshare, https://doi.org/10.6084/m9.figshare.10052426.v2). Overall attrition exceeded 15% in 54% of trials (figure S3 available from Figshare). Characteristics of trials in our primary sample are shown in table 2; summarized data are available in table S1 available from Figshare.

Benefit associated with treatment assignment

Assignment to disease-modifying experimental interventions did not demonstrate statistically significant efficacy compared to placebo assignment for long-duration trials of AD (SMD −0.03, 95% CI −0.07 to 0.01), PD (SMD −0.09, 95% CI −0.32 to 0.15), ALS (SMD 0.02, 95% CI −0.25 to 0.30), or HD (SMD 0.02, 95% CI −0.27 to 0.31) (figure 2).

Risk associated with treatment assignment

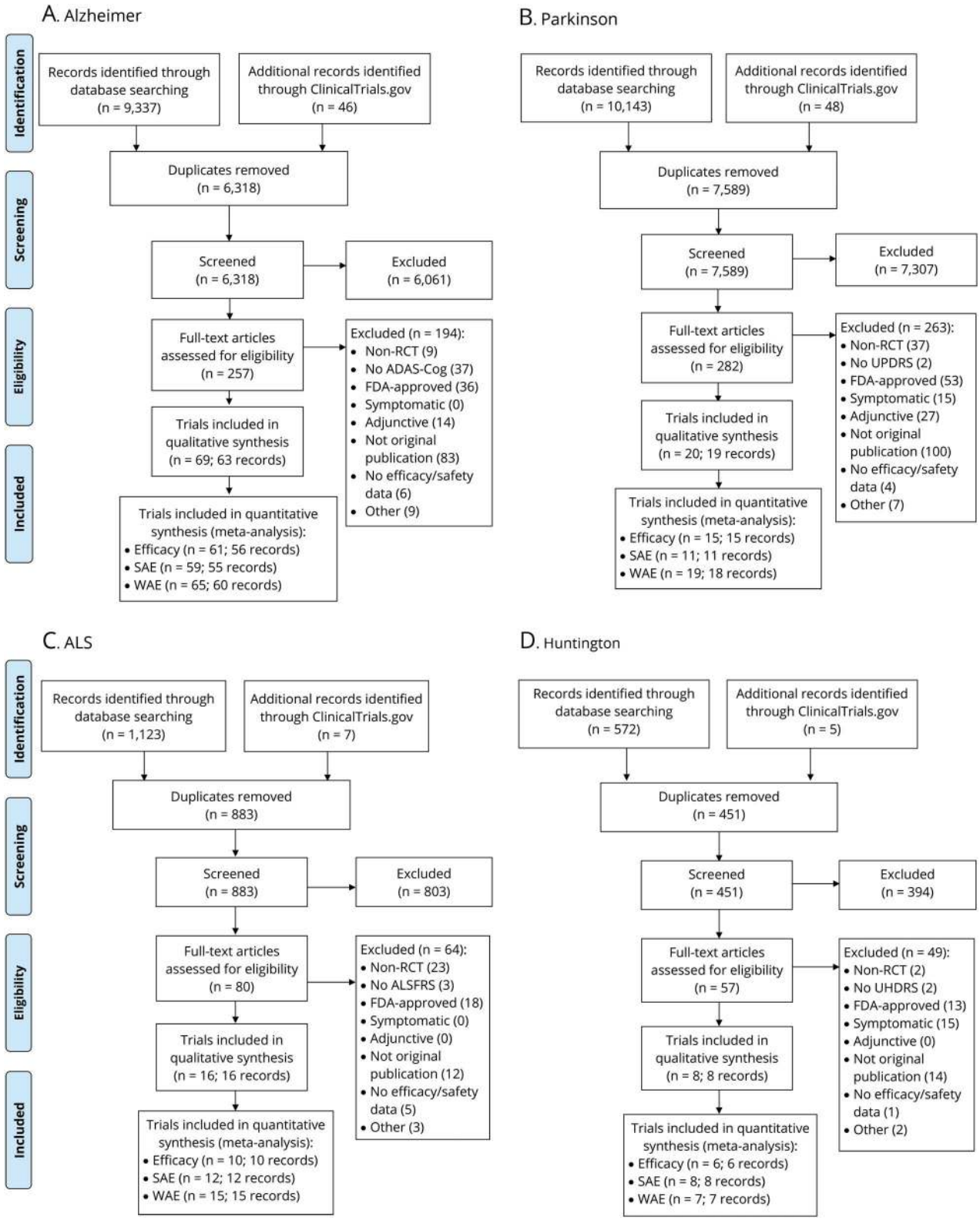
Patients assigned to disease-modifying treatment were significantly more likely to experience SAEs in long-duration AD trials (RR 1.15, 95% CI 1.04–1.27). Patients assigned to treatment had a nonstatistically significant increased risk of SAEs in PD (RR 1.32, 95% CI 0.70–2.48), ALS (RR 1.22, 95% CI 0.82–1.80), and HD (RR 1.40, 95% CI 0.50–3.89) (figure 3).The risk of WAEs was significantly higher in treatment arms for long-duration AD trials (RR 1.44, 95% CI 1.21–1.70). The RR of WAEs was not statistically significant for patients assigned to treatment in trials for PD (RR 1.35, 95% CI 0.86–2.11), ALS (RR 0.88, 95% CI 0.57–1.35), or HD (RR 1.18, 95% CI 0.41–3.37) (figure 4).

Risk and benefit in short-duration trials

The secondary analysis of short-duration trials showed a significant efficacy advantage for patients assigned to disease-modifying experimental interventions in PD (SMD −0.53, 95% CI −0.97 to −0.08) and HD (SMD −0.31, 95% CI −0.59 to −0.03) trials but not in AD (SMD −0.05, 95% CI −0.11 to 0.00) or ALS (SMD −0.11, 95% CI −0.35 to 0.12) trials (figure S4 available from Figshare, https://doi.org/10.6084/m9.figshare.10052426.v2).

Assignment to treatment was not significantly associated with greater risk of SAEs in AD (RR 0.99, 95% CI 0.71–1.38), PD (RR 0.52, 95% CI 0.23–1.19), ALS (RR 1.15, 95% CI 0.78–1.69), or HD (RR 0.76, 95% CI 0.20–2.88) (figure S5 available from Figshare, https://doi.org/10.6084/m9.figshare.10052426.v2).

Figure 1 PRISMA diagrams



Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagrams for (A) Alzheimer disease, (B) Parkinson disease, (C) amyotrophic lateral sclerosis (ALS), and (D) Huntington disease. Diagrams include trial records in both the primary (long-duration) and secondary (short-duration) samples. ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ALSFRS = ALS Functional Rating Scale; FDA = Food and Drug Administration; RCT = randomized placebo-controlled trial; SAE = serious adverse events; UHDRS = Unified Huntington's Disease Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale; WAE = withdrawal due to adverse events.

Table 2 Characteristics of trials included in the primary safety sample

	Intervention	Phase[a]	Start date[b]	Duration, wk[c]	Tx, n[d]	Plb, n[d]	Scale version[e]
Alzheimer disease							
Arai et al., 2015a/b[e1]	Vanutide cridificar	2	2009	78	54	18	11
Bayer et al., 2005[e2]	AN1792	1	2000	84	64	16	11
Brody et al., 2016[e3]	Bapineuzumab	2	2010	52	110	36	11
Coric et al., 2015[e4]	Avagacestat	2	2009	104	132	131	11
Cummings et al., 2018[e5]	Crenezumab	2	2011	73	285	146	12
Delnomdedieu et al., 2016[e6]	AAB-003	1	2010	39	69	19	11
Doody et al., 2008[e7]	Latrepirdine	2	2005	26	89	94	11
Doody et al., 2013[e8]	Semagacestat	3	2008	76	1,036	501	11
Doody et al., 2014a/b[e9]	Solanezumab	3	2009	80	1,027	1,025	11
Egan et al., 2018[e10]	Verubecestat	3	2012	78	1,358	653	11
Eli Lilly and Co, 2014[e11]	Semagacestat	3	2008	76	556	555	11
Farlow et al., 2015[e12]	CAD106	2	2008	52	47	11	11
Galasko et al., 2014[e13]	Azeliragon	2	2007	78	267	132	11
Gauthier et al., 2016[e14]	LMTM	3	2013	65	534	357	11
Gilman et al., 2005[e15]	AN1792	2	2001	52	299	73	11
Green et al., 2009[e16]	Tarenflurbil	3	2005	78	862	822	12
Honig et al., 2018[e17]	Solanezumab	3	2013	80	1,057	1,072	14
Landen et al., 2013[e18]	Ponezumab	1	NR	52	26	11	NA
Landen et al., 2017a/b[e19]	Ponezumab	2	2008	81	140	58	11
Landen et al., 2017c[e20]	Ponezumab	2	2009	78	24	12	NA
Lovestone et al., 2015[e21]	Tideglusib	2	2011	26	222	85	15
Nave et al., 2017[e22]	Sembragiline	2	2012	52	361	181	11
Ostrowitzki et al., 2017[e23]	Gantenerumab	3	2010	104	531	266	13
Pasquier et al., 2016[e24]	Vanutide cridificar	2	2007	78	184	61	NA
Rafii et al., 2018[e25]	AAV2-NGF	2	2009	104	26	23	11
Rinne et al., 2010[e26]	Bapineuzumab	2	2005	78	20	8	NA
Salloway et al., 2009[e27]	Bapineuzumab	2	2005	78	124	110	12
Salloway et al., 2014a/b[e28]	Bapineuzumab	3	2007	78	1,480	972	11
Schneider et al., 2013[e29]	Edonerpic	2	2008	52	190	183	11
Schneider et al., 2017[e30]	Edonerpic	2	2014	52	324	158	11
Sevigny et al., 2008[e31]	MK-677	2	2003	52	282	281	11
van Dyck et al., 2016[e32]	Vanutide cridificar	2	2011	86	42	21	13
Vandenberghe et al., 2016a/b[e33]	Bapineuzumab	3	2008	78	1,202	787	11
Vandenberghe et al., 2017[e34]	CAD106	2	2010	78	106	15	12
Wilcock et al., 2008[e35]	Tarenflurbil	2	2003	52	139	71	11
Parkinson's							
Devos et al., 2014[e36]	Deferiprone	3	2009	26	21	19	NA[f]

Continued

Table 2 Characteristics of trials included in the primary safety sample *(continued)*

	Intervention	Phase[a]	Start date[b]	Duration, wk[c]	Tx, n[d]	Plb, n[d]	Scale version[e]
Gross et al., 2011[e37]	RPE cells	2	2002	52	39	37	Motor (off)
Lang et al., 2006[e38]	Liatermin	2	NR	26	17	17	Motor (off)
LeWitt et al., 2011[e39]	AAV2-GAD	2	2008	26	22	23	Motor (off)
Marks et al., 2010[e40]	AAV2-neurturin	2	2006	52	38	20	Motor (off)
NINDS Investigators, 2007[e41]	GPI-1485	2	2004	52	71	71	Total 1–3[g]
Olanow et al., 2006[e42]	Omigapil	NR	2002	78	230	71	Total 2/3[g]
Olanow et al., 2009[e43]	Rasagiline	3	2005	36	581	595	Total 1–3[g]
Olanow et al., 2015[e44]	AAV2-neurturin	2	2009	104	24	27	Motor (off)
Parkinson Study Group, 2007[e45]	CEP-1347	3	2002	95	615	191	Total 1–3[g]
Stocchi et al., 2017[e46]	Preladenant	3	2010	26	614	204	Total 2/3[g]
ALS							
Lenglet et al., 2014[e47]	Olesoxime	3	2009	39	259	253	NA
Meininger et al., 2017[e48]	Ozanezumab	2	2012	48	152	151	Revised
Miller et al., 2007[e49]	Omigapil	3	NR	44	442	111	NA
Miller et al., 2015[e50]	NP001	2	2011	25	94	42	Revised
Pascuzzi et al., 2010[e51]	Talampanel	2	NR	39	40	19	Original
Sorenson et al., 2008[e52]	IGF-1	3	2003	104	167	163	Revised
Huntington's							
de Yebenes et al., 2011[e53]	Pridopidine	3	2008	26	293	144	TMS
HORIZON investigators, 2013[e54]	Latrepirdine	3	2009	26	200	203	N/A
Reilmann et al., 2017[e55]	Pridopidine	2	2014	26	326	82	TMS
Stout et al., 2015[e56]	PBT2	2	2012	26	74	35	TMS

Abbreviations: HORIZON = Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly; IGF = Insulin-like growth factor 1; NA = not applicable; NR = not reported; Plb = placebo; RPE = retinal pigment epithelium; Tx = treatment.
Characteristics of all long-duration trials (>24 weeks) included in either the serious adverse events or withdrawal due to adverse events primary analyses. Superscripts correspond to full citations in the e-References. Letters following the publication year are used to differentiate between either multiple studies within the same publication or multiple publications from the same year; these correspond to the study labels in figures 2 through 4.
[a] Phase taken as the highest phase for multiphase trials (e.g., a phase 1/2 trial would be considered phase 2).
[b] Year of enrollment start date as reported in the publication or ClinicalTrials.gov record.
[c] Weeks from baseline measurement to reported primary endpoint or time point of efficacy data extraction if different. For delayed start and crossover studies, this represents the time point at which data were extracted (i.e., the latest time point prior to switching).
[d] n Represents the total number of patients randomized to a treatment or placebo arm. Arms with multiple doses or schedules were combined by use of inverse variance weighting. Control arms were included only if patients received the same background care as the treatment arm; for example, in a 3-arm trial testing novel drug A vs standard of care B vs A + B, we extracted only the information for arms A + B (treatment) and B (control).
[e] Version of the scale for which efficacy data was extracted. ADAS-Cog for Alzheimer disease; UPDRS for Parkinson disease; ALSFRS for ALS; UHDRS for Huntington disease. NA indicates trials not included in the primary efficacy analysis due to missing data if no other reason is specified.
[f] Trial excluded from efficacy analysis despite available data because patients were on dopaminergic medication but not yet experiencing motor fluctuations and thus could not be considered to be in the "off" state.
[g] Previously untreated patients not yet experiencing motor fluctuations.

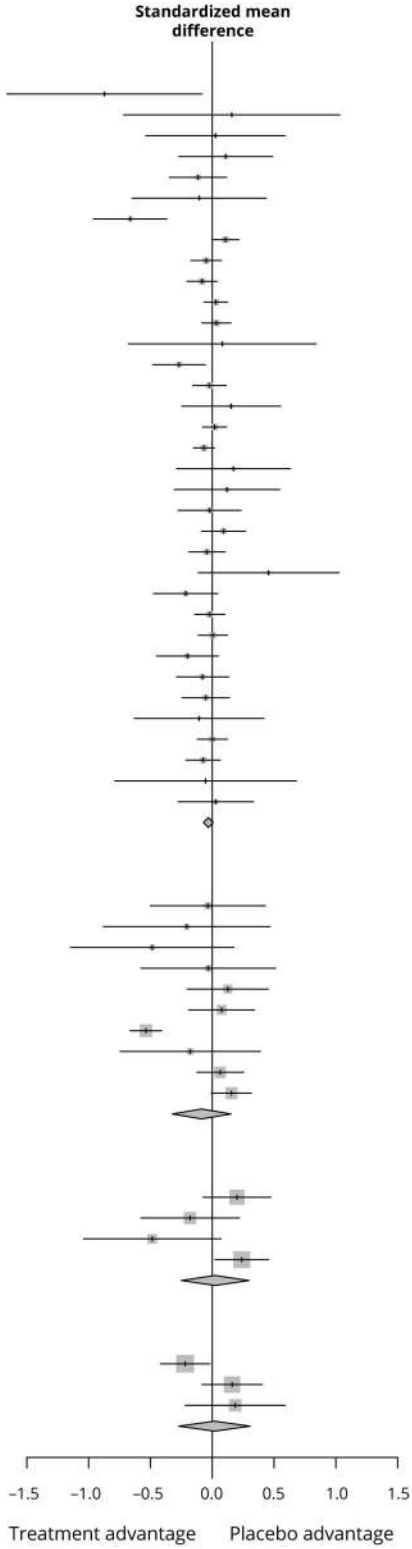
The risk of WAEs for patients assigned to treatment was significantly higher in short-duration AD trials (RR 1.53, 95% CI 1.09–2.14) but was not significantly higher than the risk for patients receiving placebo in PD (RR 1.48, 95% CI 0.61–3.55), ALS (RR 1.22, 95% CI 0.60–2.49), or HD (RR 0.91, 95% CI 0.37–2.24) trials (figure S6 available from Figshare).

Effect of trial duration

Meta-regression of treatment efficacy advantage in all 4 indications with the covariate of trial duration revealed a significant interaction with a stronger treatment advantage in shorter trials compared to longer trials ($p = 0.01$, $r^2 = 9.27\%$). For each indication individually, no significant correlations were found, but all 4 indications exhibited the same trend: treatment advantage decreased as trial duration increased (figure 5). Meta-regression showed no significant correlations between trial duration and the comparative risk of SAEs ($p = 0.87$) or WAEs ($p = 0.80$).

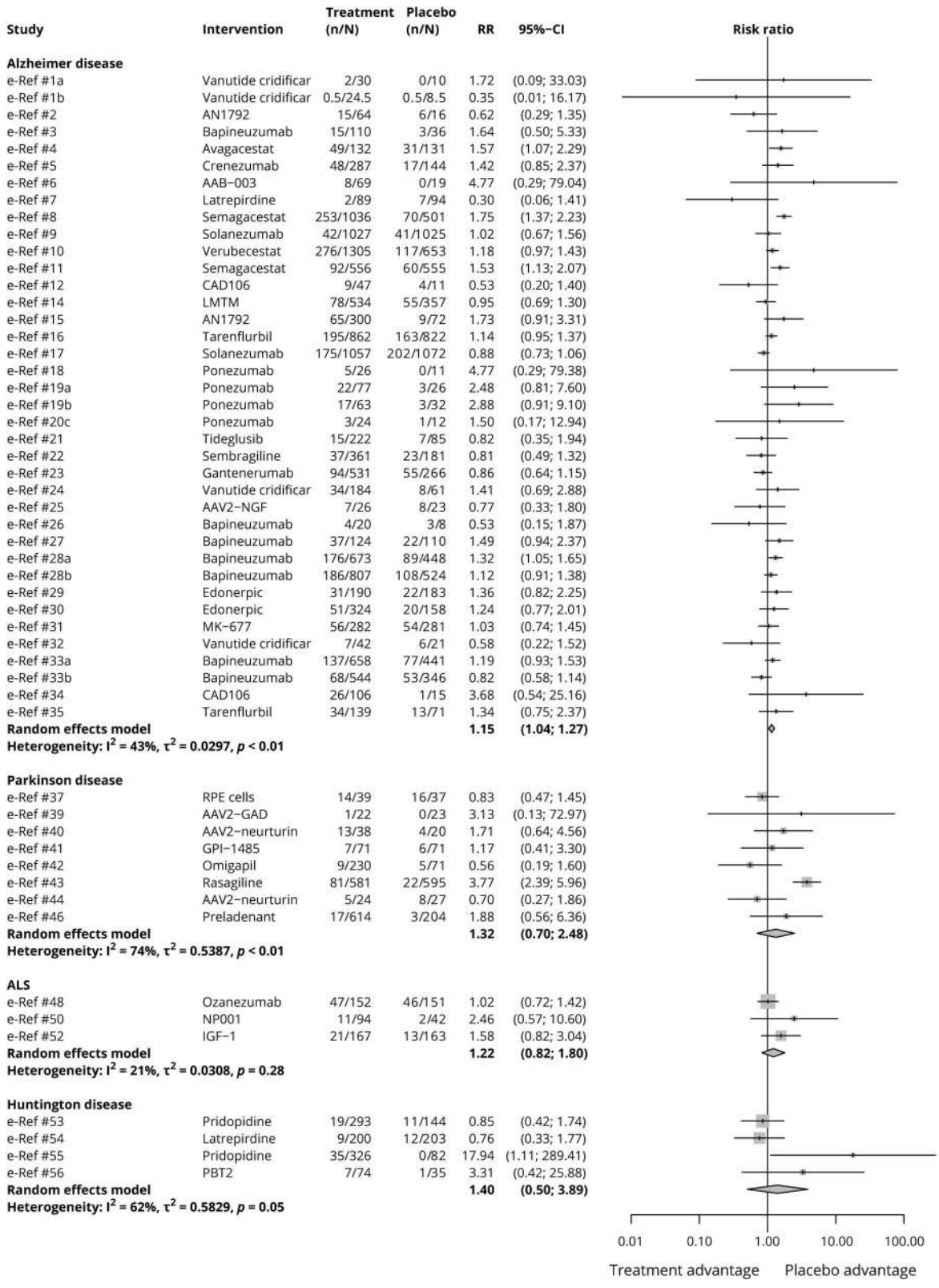
Figure 2 Benefit associated with treatment assignment

Study	Intervention	Treatment Total	Treatment Mean	Treatment SD	Placebo Total	Placebo Mean	Placebo SD	SMD	95%–CI
Alzheimer disease									
e-Ref #1a	Vanutide cridificar	26	0.59	4.13	9	4.77	6.12	−0.87	(−1.66; −0.08)
e-Ref #1b	Vanutide cridificar	18	3.23	4.39	7	2.33	7.78	0.16	(−0.72; 1.03)
e-Ref #2	AN1792	62	4.43	8.2	15	4.21	8.09	0.03	(−0.54; 0.59)
e-Ref #4	Avagacestat	45	3.15	5.57	66	2.52	5.85	0.11	(−0.27; 0.49)
e-Ref #5	Crenezumab	210	8.31	8.2	109	9.25	8.19	−0.11	(−0.35; 0.12)
e-Ref #6	AAB−003	56	0.86	5.37	17	1.4	3.95	−0.11	(−0.65; 0.44)
e-Ref #7	Latrepirdine	89	−1.9	4.98	94	2.1	6.83	−0.66	(−0.96; −0.37)
e-Ref #8	Semagacestat	980	7.65	11.91	486	6.4	10.8	0.11	(0.00; 0.22)
e-Ref #9a	Solanezumab	504	3.8	14.32	506	4.5	14.35	−0.05	(−0.17; 0.07)
e-Ref #9b	Solanezumab	518	5.3	15.68	517	6.6	15.66	−0.08	(−0.20; 0.04)
e-Ref #10	Verubecestat	1,305	7.94	8.67	653	7.7	7.67	0.03	(−0.07; 0.12)
e-Ref #11	Semagacestat	555	7.37	18.61	553	6.77	16.93	0.03	(−0.08; 0.15)
e-Ref #12	CAD106	40	5.6	7.2	8	5	7.3	0.08	(−0.68; 0.84)
e-Ref #13	Azeliragon	250	9.64	8.48	130	11.94	8.62	−0.27	(−0.48; −0.06)
e-Ref #14	LMTM	507	6.11	9.69	348	6.32	9.57	−0.02	(−0.16; 0.11)
e-Ref #15	AN1792	44	3.8	7.8	53	2.7	6.5	0.15	(−0.25; 0.55)
e-Ref #16	Tarenflurbil	840	7.27	10.52	809	7.08	9.24	0.02	(−0.08; 0.12)
e-Ref #17	Solanezumab	1,053	6.65	11.68	1067	7.44	11.76	−0.07	(−0.15; 0.02)
e-Ref #19a	Ponezumab	75	8.85	10.77	24	6.98	10.88	0.17	(−0.29; 0.63)
e-Ref #19b	Ponezumab	63	9.15	11.06	32	7.85	10.24	0.12	(−0.31; 0.55)
e-Ref #21	Tideglusib	212	1.56	6.91	82	1.7	6.9	−0.02	(−0.28; 0.23)
e-Ref #22	Sembragiline	361	5.55	7.56	181	4.86	7.62	0.09	(−0.09; 0.27)
e-Ref #23	Gantenerumab	531	5.33	10.64	266	5.77	10.19	−0.04	(−0.19; 0.10)
e-Ref #25	AAV2−NGF	26	14.52	12.12	23	9.11	11.15	0.46	(−0.11; 1.02)
e-Ref #27	Bapineuzumab	122	6.36	9.38	107	8.49	10.42	−0.21	(−0.47; 0.05)
e-Ref #28a	Bapineuzumab	658	8.5	10.26	432	8.7	10.39	−0.02	(−0.14; 0.10)
e-Ref #28b	Bapineuzumab	621	7.45	10.57	493	7.4	11.1	0.00	(−0.11; 0.12)
e-Ref #29	Edonerpic	117	1.6	6.6	132	3	7.3	−0.20	(−0.45; 0.05)
e-Ref #30	Edonerpic	232	7.26	8.14	137	7.91	8.51	−0.08	(−0.29; 0.13)
e-Ref #31	MK−677	205	3.81	14.55	209	4.57	14.49	−0.05	(−0.24; 0.14)
e-Ref #32	Vanutide cridificar	42	1.08	4.42	21	1.56	4.65	−0.11	(−0.63; 0.42)
e-Ref #33a	Bapineuzumab	650	7.32	9.94	431	7.31	9.76	0.00	(−0.12; 0.12)
e-Ref #33b	Bapineuzumab	508	7.03	11.47	328	7.88	11.59	−0.07	(−0.21; 0.07)
e-Ref #34	CAD106	65	6.6	9.23	8	7.1	8.25	−0.05	(−0.79; 0.68)
e-Ref #35	Tarenflurbil	128	4.88	6.94	61	4.68	6.77	0.03	(−0.28; 0.33)
Random effects model		**11,718**			**8,414**			**−0.03**	**(−0.07; 0.01)**
Heterogeneity: I^2 = 33%, τ^2 = 0.0038, p = 0.03									
Parkinson disease									
e-Ref #37	RPE cells	35	−10.5	10.26	36	−10.1	12.26	−0.03	(−0.50; 0.43)
e-Ref #38	Liatermin	17	−4.28	10.71	17	−1.98	11.01	−0.21	(−0.88; 0.47)
e-Ref #39	AAV2−GAD	16	−8.1	6.8	21	−4.7	6.87	−0.49	(−1.15; 0.17)
e-Ref #40	AAV2−neurturin	37	−7.21	9.49	20	−6.91	9.48	−0.03	(−0.58; 0.51)
e-Ref #41	GPI−1485	71	7.41	8.83	71	6.31	8.47	0.13	(−0.20; 0.46)
e-Ref #42	Omigapil	224	8.91	17.83	71	7.6	15.5	0.08	(−0.19; 0.34)
e-Ref #43	Rasagiline	509	1.19	5.74	487	4.27	5.74	−0.54	(−0.66; −0.41)
e-Ref #44	AAV2−neurturin	23	−7	9.92	25	−5.2	10.01	−0.18	(−0.75; 0.39)
e-Ref #45	CEP−1347	424	9.09	9.93	145	8.46	9.09	0.06	(−0.12; 0.25)
e-Ref #46	Preladenant	597	−0.86	8.65	195	−2.2	8.52	0.16	(−0.01; 0.32)
Random effects model		**1,953**			**1,088**			**−0.09**	**(−0.32; 0.15)**
Heterogeneity: I^2 = 85%, τ^2 = 0.1060, p < 0.01									
ALS									
e-Ref #48	Ozanezumab	101	10.4	6.43	104	9.1	6.53	0.20	(−0.07; 0.47)
e-Ref #50	NP001	79	3.91	4.38	35	4.7	4.28	−0.18	(−0.58; 0.22)
e-Ref #51	Talampanel	39	7.1	6.2	19	10.1	5.9	−0.48	(−1.04; 0.07)
e-Ref #52	IGF−1	167	32.89	11.77	163	29.91	13.06	0.24	(0.02; 0.46)
Random effects model		**386**			**321**			**0.02**	**(−0.25; 0.30)**
Heterogeneity: I^2 = 63%, τ^2 = 0.0472, p = 0.04									
Huntington disease									
e-Ref #53	Pridopidine	293	−0.14	8.68	144	1.77	8.69	−0.22	(−0.42; −0.02)
e-Ref #55	Pridopidine	316	−3.34	9.06	81	−4.79	8.91	0.16	(−0.08; 0.40)
e-Ref #56	PBT2	72	0.19	8.25	35	−1.3	7.3	0.19	(−0.22; 0.59)
Random effects model		**681**			**260**			**0.02**	**(−0.27; 0.31)**
Heterogeneity: I^2 = 71%, τ^2 = 0.0450, p = 0.03									



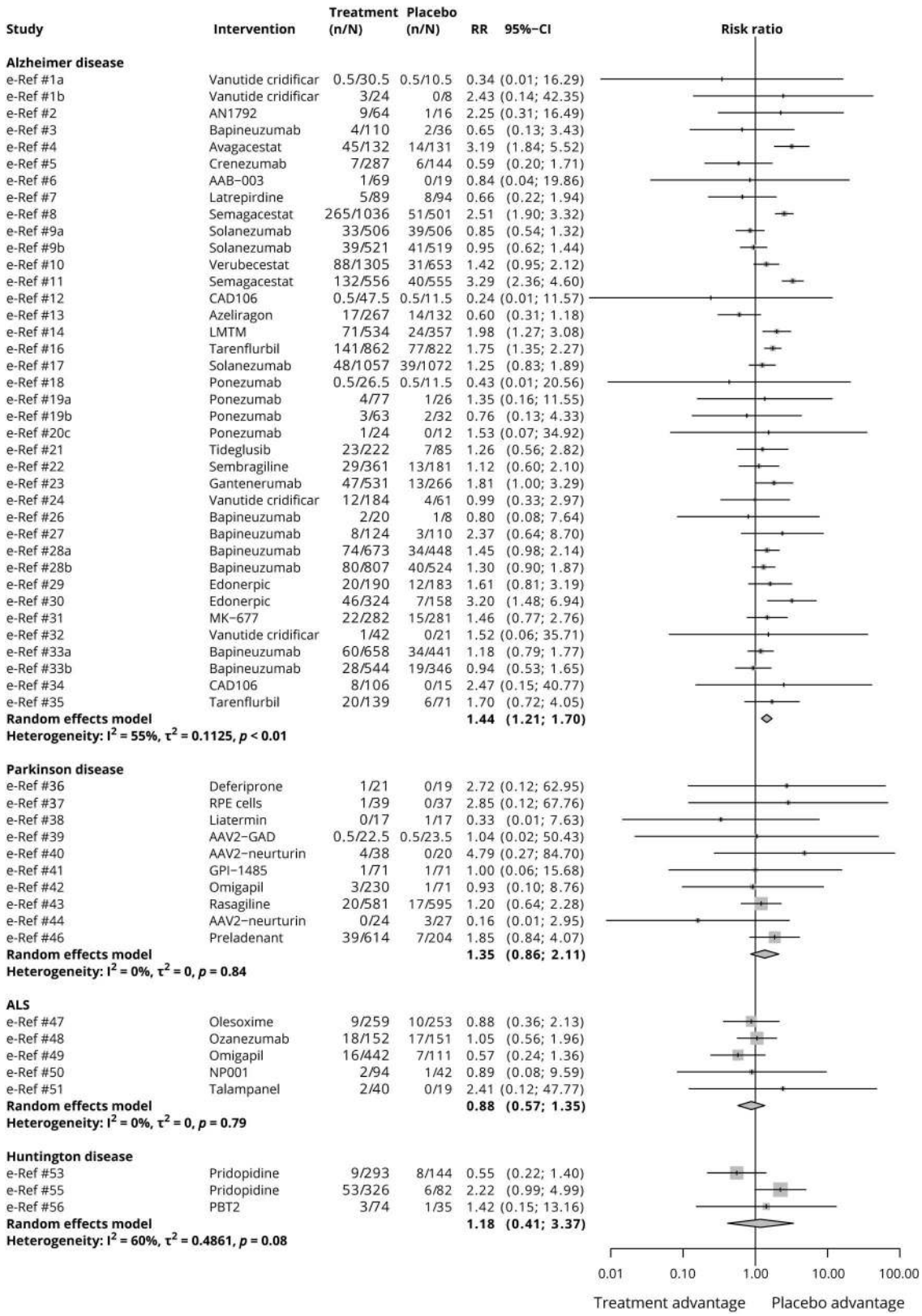
Standardized mean difference between treatment and control groups on disease-specific efficacy scales (Alzheimer disease: Alzheimer's Disease Assessment Scale–Cognitive Subscale; Parkinson disease: Unified Parkinson's Disease Rating Scale; amyotrophic lateral sclerosis [ALS]: ALS Functional Rating Scale; Huntington disease: Unified Huntington's Disease Rating Scale–Total Motor Score) in long-duration trials (>24 weeks). Note that, for clarity, all the scales are represented such that a positive mean change represents a worsening, regardless of the original directionality of the scale. Letters following the e-reference number are used to differentiate between either multiple studies within the same publication or multiple publications from the same year. CI = confidence interval; SMD = standardized mean difference. e-References are available on FigShare, https://doi.org/10.6084/m9.figshare.10052426.v2.

Figure 3 Risk of SAEs associated with treatment assignment



Risk ratio (RR) of serious adverse events (SAEs) in long-duration trials (>24 weeks) of Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis (ALS), and Huntington disease (n represents the number of SAEs; N represents the number of patients randomized). A correction factor of 0.5 was added for trials with no SAEs in either the treatment or placebo arm. Letters following the e-reference number are used to differentiate between either multiple studies within the same publication or multiple publications from the same year. CI = confidence interval. e-References are available on FigShare, https://doi.org/10.6084/m9.figshare.10052426.v2.

Figure 4 Risk of WAEs associated with treatment assignment



Risk ratio (RR) of withdrawals due to adverse events (WAEs) in long-duration trials (>24 weeks) (n represents the number of WAEs; N represents the number of patients randomized). A correction factor of 0.5 was added for trials with no WAEs in either the treatment or placebo arm. Letters following the e-reference number are used to differentiate between either multiple studies within the same publication or multiple publications from the same year. ALS = amyotrophic lateral sclerosis; CI = confidence interval. e-References are available on FigShare, https://doi.org/10.6084/m9.figshare.10052426.v2.

Effect of trial phase

Subgroup analysis of phase 2 and phase 3 trials showed no significant differences in efficacy treatment advantage between phases in AD ($p = 0.29$), PD ($p = 0.43$), ALS ($p = 0.57$), or HD ($p = 0.24$). Significant differences in safety were found between phase 2 and 3 PD trials with a trend toward larger treatment disadvantages in phase 3 on both measures of SAEs ($p < 0.01$) and WAEs ($p = 0.01$). In ALS, assignment to treatment in phase 3 trials was associated with significantly lower risk of WAEs ($p = 0.01$). No significant advantages on safety measures were found between phase 2 and 3 trials in the other indications with respect to SAEs or WAEs (table S2 available from Figshare, https://doi.org/10.6084/m9.figshare.10052426.v2).

Sensitivity analyses

Samples derived from modified definitions of disease-modifying treatments showed no significant differences from the primary results in the intent-based or mechanism-based analyses (table S3 available from Figshare, https://doi.org/10.6084/m9.figshare.10052426.v2). Comparison of pooled and high-dose arms showed no significant differences from the primary analysis on efficacy, SAEs, or WAEs in any indication (table S4 available from Figshare). Comparing method of imputation (last observation carried forward vs mixed model repeated measures vs observed cases) in the AD sample revealed no significant differences; this analysis was not performed for the other 3 indications because of the limited number of trials available for analysis (table S5 available from Figshare). Stratification by attrition rate (<15% vs ≥ 15%) revealed a significant difference in SAE risk for AD, with high-attrition trials presenting a significantly higher risk for patients assigned to treatment. No other significant differences in treatment advantage were found between high- and low-attrition trials (table S6 available from Figshare).

Discussion

Our findings suggest that, on the whole, patients assigned to investigational treatment are no better off than patients assigned to placebo in RCTs testing unapproved, disease-modifying interventions. Across all 4 indications, patients assigned to investigational treatment did not experience better efficacy outcomes; no SMDs were statistically significant, and the largest treatment advantage of −0.09 in PD did not meet the threshold for a small effect size by Cohen criteria,[38] thus bringing into question any potential efficacy. Patients assigned to investigational treatment were more likely to experience SAEs in all 4 indications; however, statistical significance was seen only in AD, and even so, the safety advantages of placebo assignment were slight. The SAE and WAE risk differences correspond to NNTHs of 33 patients for SAEs (95% CI 20–100) and 33 patients for WAEs (95% CI 20–50). In comparison, a meta-analysis of RCTs testing approved cholinesterase inhibitors for AD found NNTHs of 12 for all adverse events and 16 for WAEs.[39]

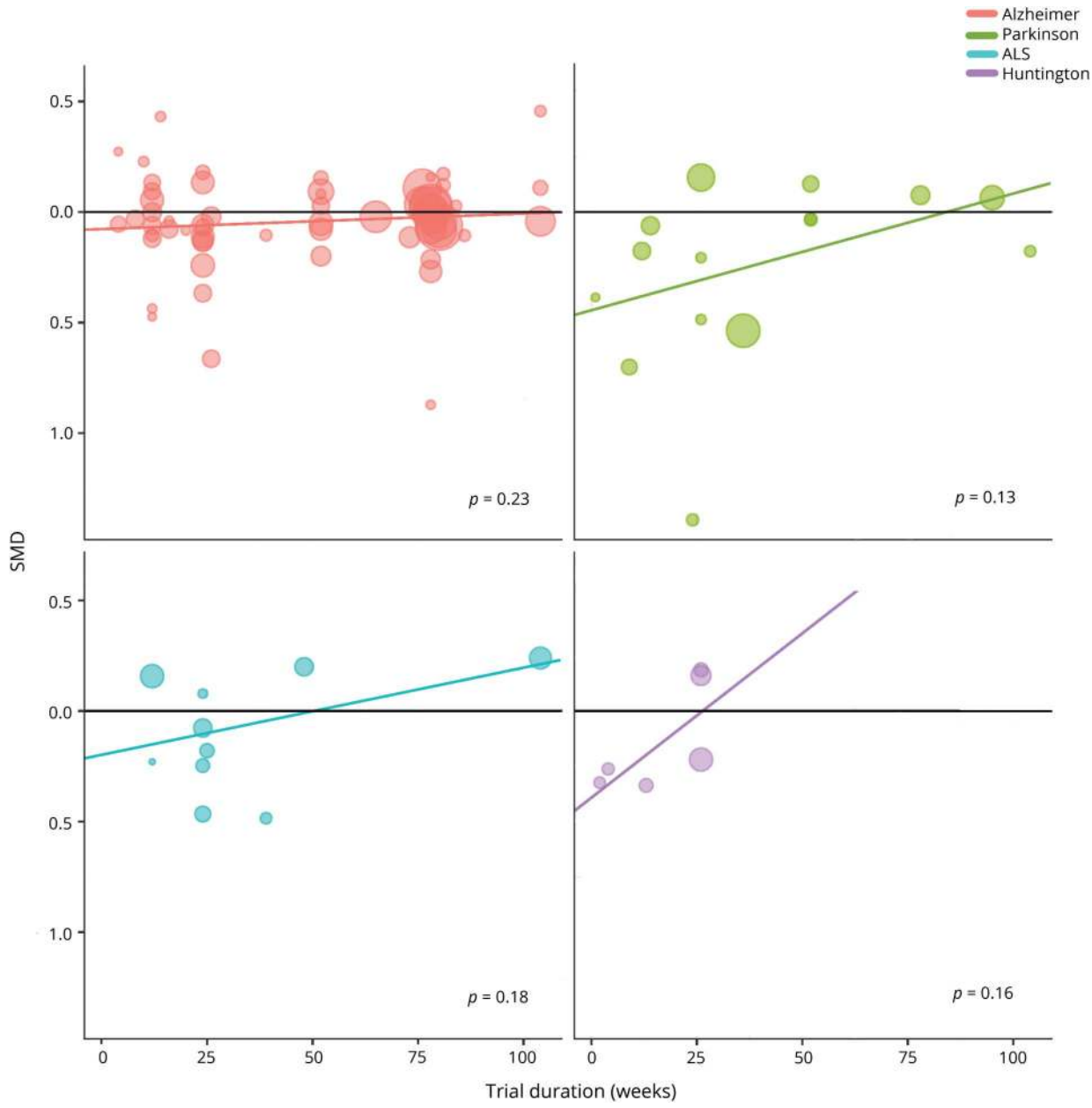
In short-duration trials, assignment to investigational treatment proved advantageous in PD and HD, with AD and ALS also trending toward a treatment advantage. The discrepancy in the observed benefit between short- and long-duration trials might have 2 explanations. First, it could reflect a regression to the mean from the selection of only those compounds that show large effects in the short term for longer-term testing. Second, it could reflect that compounds have symptomatic effects in the short term. Patient expectations may be heightened by large effect sizes in earlier-phase trials. Our data on the long-term effects caution against such heightened expectations.

What do these results mean for patients pursuing access to treatments through trial participation or expanded access and the clinicians guiding them through these processes? Patients with neurodegenerative diseases may be willing to endure high levels of risk to access unproven, putatively disease-modifying treatments through trials or expanded access.[40] Furthermore, clinicians may prescribe treatments with unfavorable risk/benefit profiles because of patient demand or a desire to help distressed patients, especially when the alternative is palliative care. Our findings do not rule out that some individual patients derive benefits from accessing investigational treatments, nor do they exclude the possibility that, at some point in the future, some patients will benefit by accessing an unapproved treatment. They do, however, provide evidentiary grounds for clinicians to temper patient expectations in informed consent discussions. If disease-modifying treatments had large benefits for a small number of patients or small benefits for a larger number of patients, one might expect the substantially greater statistical power afforded by this meta-analysis to detect an advantage for treatment assignment. Instead, we observed none.

Numerous recent initiatives have sought to lower barriers to accessing investigational treatments for patients. These include the US FDA's Expanded Access Program, which enables patients with serious or life-threatening conditions who are ineligible for trial participation to access unapproved therapies for which the potential benefit justifies the risk.[41] Over the last 5 years, >9,000 applications have been approved.[42] National right-to-try legislation, which attempts to bypass FDA oversight altogether, requires only that a drug have completed a phase 1 trial.[43] Our findings of a lack of advantage associated with treatment assignment for patients in phase 3 compared to phase 2 trials suggest the fallibility of inferring treatment benefit from early-phase trial evidence. Recent high-profile failures such as a string of negative late-phase trials of antiamyloid agents in AD reinforce the need for cautious interpretation of early-phase results and for balanced reporting in publications, academia and industry press releases, and the media.[44] Furthermore, our findings support the obvious point that regulatory approval standards have, on balance, prevented patients with debilitating illnesses from being further burdened by the side effects of ineffective treatments. The value of early access policies on improving outcomes for patients is uncertain.

Our study has limitations. First, we included only trials with published results. Many trials testing novel neurology drugs are

Figure 5 Correlation between efficacy and trial duration



Meta-regression of efficacy with covariate of trial duration. Effect size represents the standardized mean difference (SMD) between the treatment and placebo arms; a positive SMD indicates a trial that favored the placebo arm. The *p* values correspond to the slope of the regression line. The r^2 values were 4.96%, 0.27%, 0.14%, and 19.40% for Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis (ALS), and Huntington disease, respectively.

never published.[45] An example is the drug latrepirdine: our sample included the positive phase 2 AD trial of this drug,[46] but the nonpositive phase 3 data were not available.[47] Publication biases would most likely lead to an overestimate of benefit and underestimate of risk associated with treatment assignment. A second limitation is the heterogeneity of trials. However, our study did not set out to estimate risk and benefit for a sample of patients exposed to the same treatment; our aggregate estimates should therefore be understood as providing a general description of the risk and benefit to patients in clinical trials for neurodegenerative disease. Finally, the sample of PD, ALS, and HD trials captured in our search was small and hence underpowered to detect modest or small advantages or disadvantages associated with treatment assignment. This limits our ability to draw firm conclusions for these conditions.

Our analysis may be useful to clinicians looking to provide reassurance to patients who fear missing out on therapeutic benefit through randomization to placebo, trial ineligibility, or lack of expanded access programs. Surveys show that patients are apprehensive of placebos in trials and perceive

assignment to comparator arms as depriving them of clinically advantageous treatments.[48–51] Indeed, trials often attempt to overcome aversion to placebo arms by using 2:1 randomization ratios.[52] Our findings indicate that this practice is unnecessary and potentially disadvantageous to patients. Those tasked with designing trials or advising patients in their choice of treatment should consider the clinical impact that experimental treatments for neurodegenerative disease have historically had on patients. Our meta-analysis suggests that, over the last 15 years of testing, neither patients assigned to placebo arms nor patients deprived of investigational treatments due to drug regulations have suffered medically by lack of access; if anything, they may have been slightly better off.

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Disclosure

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Appendix Authors

Name	Location	Role	Contribution
Aden C. Feustel, BSc	McGill University, Montreal, Quebec, Canada	Co–first author	Piloted the study; performed the literature search, eligibility screening, and data collection; revised the manuscript
Amanda MacPherson, BSc	McGill University, Montreal, Quebec, Canada	Co–first author	Performed the literature search, eligibility screening, and data collection; analyzed the data; drafted the manuscript
Dean A. Fergusson, PhD	Ottawa Hospital Research Institute, Ontario, Canada	Coauthor	Consulted on questions relating to the statistical analysis plan and data interpretation; revised the manuscript
Karl Kieburtz, MD	University of Rochester, NY	Coauthor	Consulted on questions relating to eligibility and data collection; revised the manuscript
Jonathan Kimmelman, PhD	McGill University, Quebec, Canada	Corresponding author	Designed and conceptualized the study; revised the manuscript; had full access to all data and had final responsibility for the decision to submit for publication

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Data available from figshare (Additional References, References e1-e55): https://doi.org/10.6084/m9.figshare.10052426.v2