Nonpublication of Trial Results for New Neurological Drugs: A Systematic Review

NOTE: This is an earlier version of the manuscript published in Annals of Neurology 2017. It contains information and data that editors/referees asked us to remove as a condition for acceptance. We strongly disagreed and therefore present those data in this version.

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ABSTRACT

Objective: To evaluate nonpublication rates among trials of new successful and unsuccessful neurological drugs.

Methods: Our 'licensed' drug cohort consisted of all novel drugs receiving FDA licensure 2005 to 2012 inclusive in seven neurological disorders. Our cohort of 'stalled' drugs included all experimental agents tested in the same domains that had at least one completed phase III trial in the same timeframe but failed to receive FDA approval. Trials of these drugs were included in our sample if their primary outcome collection occurred before October 1, 2010. We determined the publication status of eligible trials using searches of clinicaltrials.gov, Google Scholar, PubMed, Embase, sponsor websites, and direct electronic query of trial contacts and sponsors. The primary outcome was journal publication (or results reporting in other media).

Results: The unadjusted proportion of published trials of licensed drugs was 56% (91/163), vs. 32% (64/203) for stalled drugs in our sample. The adjusted hazard ratio for publication was 1.79 (95% confidence interval 1.20 to 2.67) in favour of licensed drugs. 14,092 and 33,882 volunteers participated in unpublished trials of licensed and stalled neurological drugs, respectively. Result data were not publicly available in any form for 10% (16/163) and 46% (94/203) of trials of licensed and stalled drugs, respectively.

Interpretation: Results of trials for stalled drugs are heavily underreported. This deprives research and care communities of evidence about pathophysiology, drug class effects, and the value of surrogate endpoints in trials.

INTRODUCTION

Neurological diseases exact immense and growing burdens on society.[1-3] Unfortunately, neurological drug development requires larger financial and time commitments compared to many other fields[4] and remains highly failure-prone, with only 9% of agents put into trials advancing to regulatory licensure.[5] As a consequence, many pharmaceutical companies are reducing investments in neurological drug development.[6-8]

One reason why attrition is so common is that pathophysiological processes driving CNS disease are not well understood,[7] thus confounding programs of rational drug development.[9] Related to this, many neurological diseases—like Alzheimer's or Parkinson's disease—lack animal models that fully recapitulate human disease phenomena.[10-12] Against this backdrop, unsuccessful translation trajectories provide vital feedback on the biological premises, animal models, and pharmacodynamic markers that drive neurological drug development.

Information from unsuccessful translation trajectories often has implications for clinical care as well. It can provide safety information should the drug be repositioned for other indications. Moreover, treatment decisions are often informed by pathophysiological models of disease, especially in the setting of off-label prescription. For instance, the use of recombinant factor VIIa for hemorrhagic stroke was largely informed by knowledge of its mechanism of action.[13] Trials are often the most reliable way of validating these mechanistic theories.

Previous studies have indicated that many prelicensure trials are never published,[14-17] thus limiting opportunities to exploit findings from unsuccessful translation trajectories. Such nonpublication also violates human protection policies[18-19] and potentially erodes participant

trust in the research enterprise.[20,21] That subjects participating in trials of stalled neurological drugs may be suffering advanced disease, lacking decisional capacity, or may have been exposed to unsafe or ineffective products makes nonpublication still more ethically problematic.

In this study, we evaluated publication rates for trials testing a cohort of neurological drugs that reached pivotal testing before 2013. We also examined reporting of trial results through mechanisms like company repositories or trial registries.

METHODS

Our primary objective was to quantify the accessibility of results for trials of neurological drugs that recently reached phase III trials but did not receive FDA licensure ("stalled drugs"). As a basis of comparison, we quantified publication rates for a contemporaneous sample of neurological drugs receiving FDA approval ("licensed drugs"). Our study was exempt from ethics review by the McGill University Institutional Review Board based on the Tri-Council Policy Statement (2014) Articles 2.2 and 2.4. As described below, we queried contacts by email based on information from public registries for confirmation about the availability of published trial results. However, we did not elicit confidential information or individual identifiable or coded data.

Drug selection

We selected the six most debilitating neurological conditions by Disability-Adjusted Life Years according to the World Health Organization[22]: 1) stroke; 2) migraine; 3) epilepsy; 4) dementias (from which we selected the most common form,[23] Alzheimer's disease); 5) Parkinson's disease;

6) multiple sclerosis. Our licensed drug cohort consisted of all new molecular entities (NMEs) that received FDA licensure in the above six indications between January 1, 2005 and December 31, 2012. Approved NMEs were identified from FDA licensure documents[24] and cross-referenced with Centerwatch.com.[25] Because neurological drug approvals were limited and an insomnia drug had been licensed in our timeframe, we added insomnia as a seventh indication. The time window for licensed drug eligibility in our study was constrained on one side by the need for a recent sample with a substantial volume of registered trials, and on the other side by the need for sufficient follow up time to allow for publication of results. NMEs must have been testing in disease-modifying treatment of the lead neurological indication, except in the case of Parkinson's disease, for which acceptable indications driving clinical development included the treatment of motor symptoms and levodopa-induced dyskinesia.

The stalled drug cohort was created to capture unsuccessful NMEs that were contemporaneously pursued. We searched clinicaltrials.gov using MeSH synonym strings for all experimental agents that reached phase III testing in each of the seven disease domains. Captured interventions were screened and synonyms consolidated. Exclusion criteria included: 1) procedures or behavioural interventions; 2) devices; 3) earliest phase III trial end date before January 1, 2005 or after December 31, 2012; 4) dietary supplements, food additives or medical food supplements; 5) herbal remedies; 6) FDA licensure in any indication; 7) publication of the first trial prior to January 1, 2000 according to PubMed (to ensure the unlicensed drug cohort reflects the recency of the licensed drug cohort).

Trial selection

To create our trial sample, we searched clinicaltrials.gov for all trials involving each drug in our two cohorts. Inclusion criteria for registered trials advanced into publication searching were: 1) core or extension studies of 2) any phase 3) registered on clinicaltrials.gov with 3) enrolment of at least one patient 4) that reported primary outcome collection end date before September 30, 2010. The current legislation[26] mandates that results for Applicable Clinical Trials of approved drugs, biologics, or devices be deposited within 12 months of the primary completion date reported in the registration record. Though no public indication is given of whether a given trial is subject to mandatory reporting or not, Miller et al[27] estimated that a median of 67% of applicable trials per drug were compliant, though compliance varied widely by company. Our previous work suggested that 95% of registered trials that publish results do so within 54 months of trial closure.[17] Therefore, we afforded 59 months between reported trial end date and our final literature search, though we subsequently allowed 4 months for our query of trial investigators and sponsors. We extracted the following information from registry entries: start and end date, indication, sponsor, final patient accrual, phase, completion status, control arms, and results on clinicaltrials.gov.

Publication status

We searched the following sources for publications and results reporting: clinicaltrials.gov, Google Scholar (using registry identifiers), PubMed and Embase (using drug name and synonyms, indication, subindication, and comparators), and sponsor websites. We confirmed publication identity by comparing sample size, trial arms, duration, dosages, administration schedules, design elements, and primary investigator. A trial was considered published if it appeared as a full journal publication. We also recorded abstract-only publications, result deposition on clinicaltrials.gov, and trial summaries on sponsor websites. We queried contacts

named in registration records when we could not find a matching full publication. The final literature search was performed by AH on August 23, 2015. Responses to queries verifying trial publication status were accepted until December 31, 2015. When information provided by registrants disagreed with our records, we sought clarification. Our queries to investigators elicited information about publicly available trial records and were thus exempted from ethical approval by the McGill University Institutional Review Board.[28]

Outcomes

Our primary outcome was the proportion of published trials of licensed and stalled drugs. Secondarily, we examined whether the rate in delay from last primary outcome data collection to the date of publication is greater for studies of licensed drugs compared to studies of stalled drugs. As prespecified subgroup analyses, we tested whether nonpublication of stalled drug trials was more frequent for studies that were entirely privately funded (by pharmaceutical or biotechnology companies), earlier phase, completed earlier than the median trial completion date, terminated/unknown in completion status, and extensions rather than core studies.

Analysis and statistics

A descriptive analysis of publication success in each cohort (stalled versus licensed) and by prespecified subgroups was performed to illustrate the proportions of trials with full journal publications in each category. Unadjusted relative risks with their 95% confidence intervals were calculated to compare between group (stalled versus licensed) proportions. For our primary analysis, the effect of licensed versus stalled drug trials on time to publication was analysed using a prespecified Cox proportional hazards model accounting for intra-cluster dependency at the drug level and for covariates such as sample size, indication, sponsor type, phase, and trial

status. We fit a Cox model from time of completion of the trial to publication, with a time-varying covariate for FDA approval. The time period for trials published before approval was considered as "unlicensed". The analysis was done using SAS (9.3) (SAS Institute, Cary, NC, USA). We tested the effect of publication success between licensed and stalled drug trials within a number of a priori subgroups including funding type, phase, trial status, and end date. A Kaplan-Meier analysis was performed post hoc to illustrate the time to publication in each cohort. We defined significance as $P \leq 0.05$ and did not correct for multiplicities. All drugs and all trials of those drugs meeting our criteria were included in the study sample. As such, no formal sample size calculation was performed.

RESULTS

Sample characteristics

Our protocol identified 8 licensed drugs and 28 stalled experimental interventions (Table 1). The drugs in the licensed and stalled cohorts were tested contemporaneously: the median delays from the end of the first phase III trial in the main neurological indication to our search were 86 and 85 months, respectively.

We identified 163 registered trials of licensed drugs and 203 registered trials of stalled drugs (Table 2) meeting eligibility. Table 3 shows the characteristics of the trials. The median time between trial closure and our publication search was 92 months for licensed drug trials (range 59–181 months) and 82 months for stalled drug trials (range 59–146 months). Licensed drugs had a mean of 20.4 trials per drug and unlicensed drugs had a mean of 7.3 trials per drug.

Availability of publications

The proportion of published registered trials of licensed drugs was 56% (91/163) vs. 32% (64/203) for trials of stalled drugs (risk ratio 1.49, 95% CI: 1.14 to 1.96). The total proportion of trial results accessible through other media (conference abstracts, registration records on clinicaltrials.gov, or sponsor summaries) was 34% for trials of licensed drugs and 22% for trials of stalled drugs (Table 4) (risk ratio 1.45, 95% CI: 1.00 to 2.00).

According to clinicaltrials.gov enrolment records, 96,483 participants enrolled in the 366 clinical trials captured by our sample. Of these, 14,056 (37%) participants in licensed drug trials and 33,882 (58%) participants in stalled drug trials enrolled in studies that were never published. 2109 (6%) and 22,102 (38%) participants in licensed and stalled drug trials, respectively, were enrolled in studies that have yet to make results available in any form.

Our adjusted hazard ratio of time to publication success demonstrated a 1.79-fold greater rate of publication for trials of licensed drugs compared to trials of stalled drugs (hazard ratio (HR): 1.79 (95% confidence interval (CI) 1.20 to 2.67)) (Figure 1).

The delay to publication from the reported end of primary outcome data collection for licensed drug trials was a median of 43 months (range 4-144 months), compared with 36.5 months (range 2-89 months) for stalled drug trials. The Kaplan-Meier estimate of time to nonpublication is depicted in Figure 2.

We queried registry contacts and sponsors about 209 trials and received responses about 145 (68%). Registrants identified one publication not captured by our search and another published after our last literature search.

Factors affecting publication

Publication rates were greater for trials of licensed drugs regardless of indication, type of funding, and completion status (Figure 1). Publication rates varied by phase: publication rates among phase I and III trials favoured licensed drugs (HR: 2.08 with 95% CI 1.09 to 3.98 and HR: 3.57 with 95% CI 1.14 to 11.18, respectively), but phase II trials demonstrated trends towards stalled drug trials. Among trials with earlier closure dates (before the sample median), publication was greater for trials of licensed drugs (HR: 1.66, 95% CI: 1.10 to 2.52), but the rates are no longer significantly different in the later trials (closing after the sample median) (HR: 1.66, 95% CI: 0.85 to 3.25).

Publication of stalled drug trials varied by sponsorship. Among companies sponsoring ten or more trials in our sample, the companies with the highest proportions of published trials were SK Life Science, UCB Pharma, and Merck. The lowest publication proportions were those of Sanofi, Merz Pharma, and Pfizer.

DISCUSSION

We used a cohort of new drugs developed for seven neurological conditions to demonstrate that the rate of publication of licensed drug trials is nearly twice higher than that of stalled drug trials. Our results are largely in agreement with a previous analysis,[17] but suggest trials of neurological drugs may have a worse record of publication than drugs in other disease domains.

Nearly half of licensed drug trials and 68% of trials for stalled products went unpublished, including pivotal studies for new drugs against Alzheimer's disease, insomnia, and Parkinson's disease. If a participant enrols in a trial of a neurological drug that reaches late stage testing, but

is never licensed, the probability that his or her data will be reflected in a trial publication is two in five.

Some results were available through other media like abstracts or public databases. According to FDAAA801,[26] result reporting is required for post-phase I trials of licensed drugs with one or more US sites, but the US Department of Health and Human Services issued a Final Rule in September 2016 expanding the scope of trials that require summary reporting to include unlicensed drugs as well.[29] However, media like registries are no substitute for publication. The latter provides greater description of methods, outcomes, and interpretation. Journal publications also are subject to quality assessment (through peer review) and are accessible through easily searchable databases like PubMed.

That so little information from unsuccessful translation trajectories is published represents a missed opportunity to put neurological drug development on more solid evidentiary footing. Results from unsuccessful translation trajectories provide feedback on preclinical models or surrogate outcomes and validate pathophysiological theories. They can also uncover drug class effects or provide insights into safety, pharmacokinetic, and pharmacodynamic parameters that might inform drug repositioning.

For instance, among the unsuccessful Alzheimer's drugs in our cohort are xaliproden and lecozotan. Both affect serotonin 1A (5-HT_{1A}) receptors[30-31] and their trials may help resolve uncertainties regarding the role of this target in countering the effects of memory loss. However, none of the five xaliproden trials and only one of the eight lecozotan trials have been published. Similarly, results from trials of the stalled drug neramexane, which is chemically related to an

approved Alzheimer's drug, memantine,[32] might inform the discovery of potential NMDA receptor antagonist class effects. However, only one of the sixteen registered trials of neramexane has been published or reported results in any form.

Nonpublication of trials in unlicensed indications also has ramifications for care. It deprives patients and healthcare systems in these jurisdictions of safety and efficacy evidence, but also of insights into fundamental disease processes. In Alzheimer's disease, bexarotene has been prescribed off-label[33] following a preclinical study demonstrating the drug's effects on soluble amyloid-beta and neuritic plaques.[34] Negative trials involving drugs that target this mechanism help inform the clinical relevance of such findings.

Notable in our sample were the differing publication rates of licensed and stalled drug trials across various phases of drug development. Though publication rates were higher for licensed drug trials in phase I and III, publication rates of phase II trials tended to favour unlicensed trials. One possible explanation is that drugs destined to stall produce spuriously large effects in phase II testing, causing these findings to be rushed into publication. Further study would be required to examine this hypothesis. To explore whether reporting improved over time, we examined the publication of trials closing before and after the median trial end date of the sample. Licensed drug trials closing earlier had much higher publication rates than stalled drug trials, but this difference was diminished for trials closing more recently. Though only a small proportion of studies had a non-industry funding component, it was also striking that such trials had a poorer publication record (40% of licensed and 29% of unlicensed drug trials) than their industry-only counterparts (59% and 32%, respectively). These data highlight an opportunity for public and

non-profit sponsors to assert their influence and to effect change by conditioning funding on a requirement to publish the results of the trial.

Limitations

Our analysis has several limitations. First, longer follow-up might capture more publications, though the flattening of the Kaplan-Meier nonpublication curves (Figure 3) after 100 months of follow-up suggests our results are unlikely to be affected by a longer follow-up time. However, an intent to publish or a reference to a manuscript in preparation was expressed by registrants in query responses for eleven trials, ten of which tested stalled drugs. Even if drug developers make good on this promise, however, the delay will still have proven costly from a scientific and ethical standpoint. Second, licensure was based on FDA approval only. We determined one licensed drug in our cohort is not EMA-approved (Ramelteon); one "stalled" drug filed for FDA approval in late 2015 and was granted EMA approval in early 2016 (brivaracetam); and another "stalled" drug is pending EMA approval (pitolisant). However, an attempt to use the EMA criteria as the basis for our sample would be confounded by Ramelteon's approval status in the United States, which makes result reporting for most of its trials mandatory despite its 'unlicensed' status as per the EMA. Third, our analyses are limited by the quality of the registration record. One trial was reported as "Completed", but when contacted, investigators listed in the registry indicated the study had never taken place. Fourth, availability of trial reports from unsuccessful translation trajectories would not guarantee the application of this information to decision-making. "Negative" studies are often underutilized in research planning.[35-36]

Conclusion

Despite their ethical and practical importance, results of trials of unlicensed drugs are heavily underreported. Nonpublication fails to satisfy ethical requirements of clinical research, erodes participant trust, and fails to provide vital feedback on drug safety, class effects, trial design, and our understanding of the underlying pathophysiology of neurological disease.

In light of rising costs of drug development and diminished pharmaceutical investment in CNS disorder-related research and development, neurological disorders face a withering pipeline and a bleak therapeutic future. To the many creative proposals that have been advanced to improve the efficiency of neurological drug development, we suggest a greater emphasis on complete and accessible trial reporting.

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Drafting text and figures: AH, JK, DF

Potential conflicts of interest

All authors declare that no competing interests exist.

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Figure 1: FDA Designation

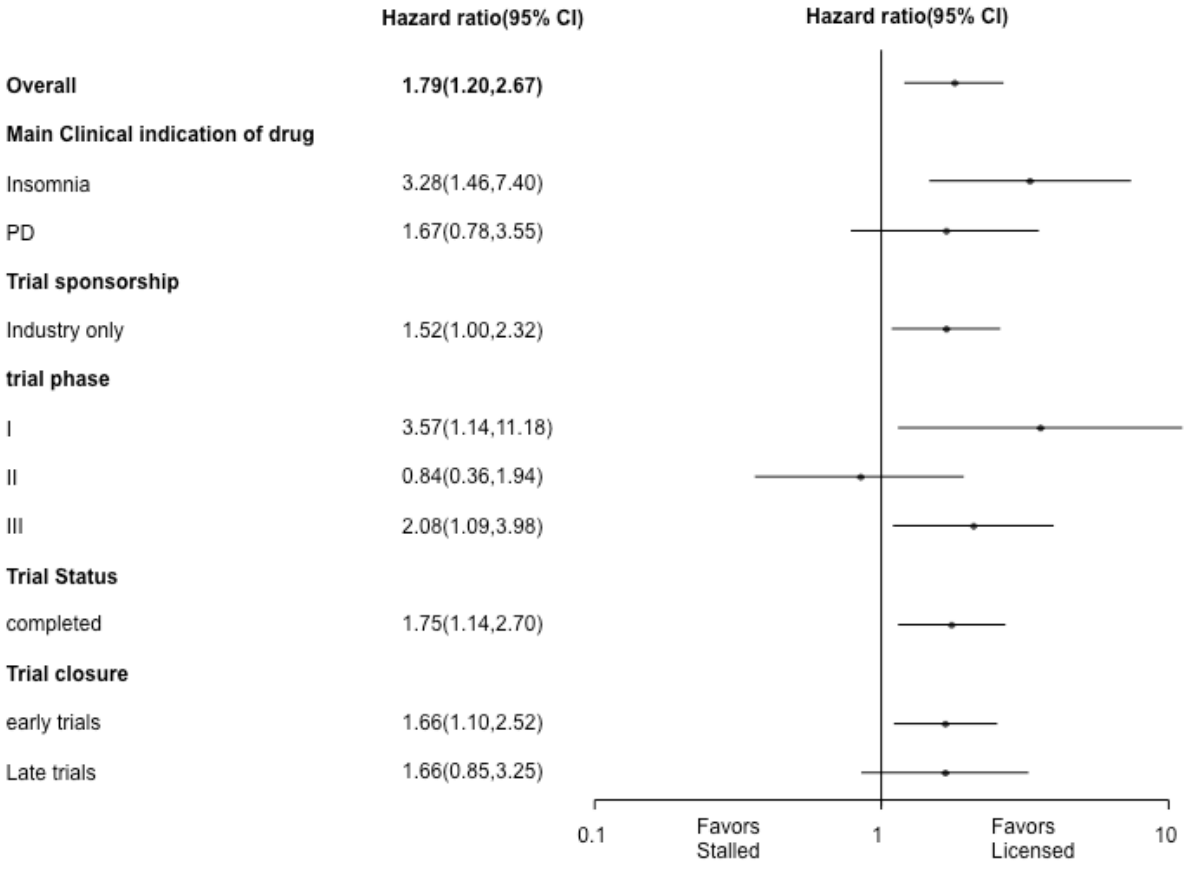

Figure 1: Hazard Ratios and 95% confidence intervals of publication of trials of licensed drugs compared with trials of stalled drugs: overall and by major subgroups.

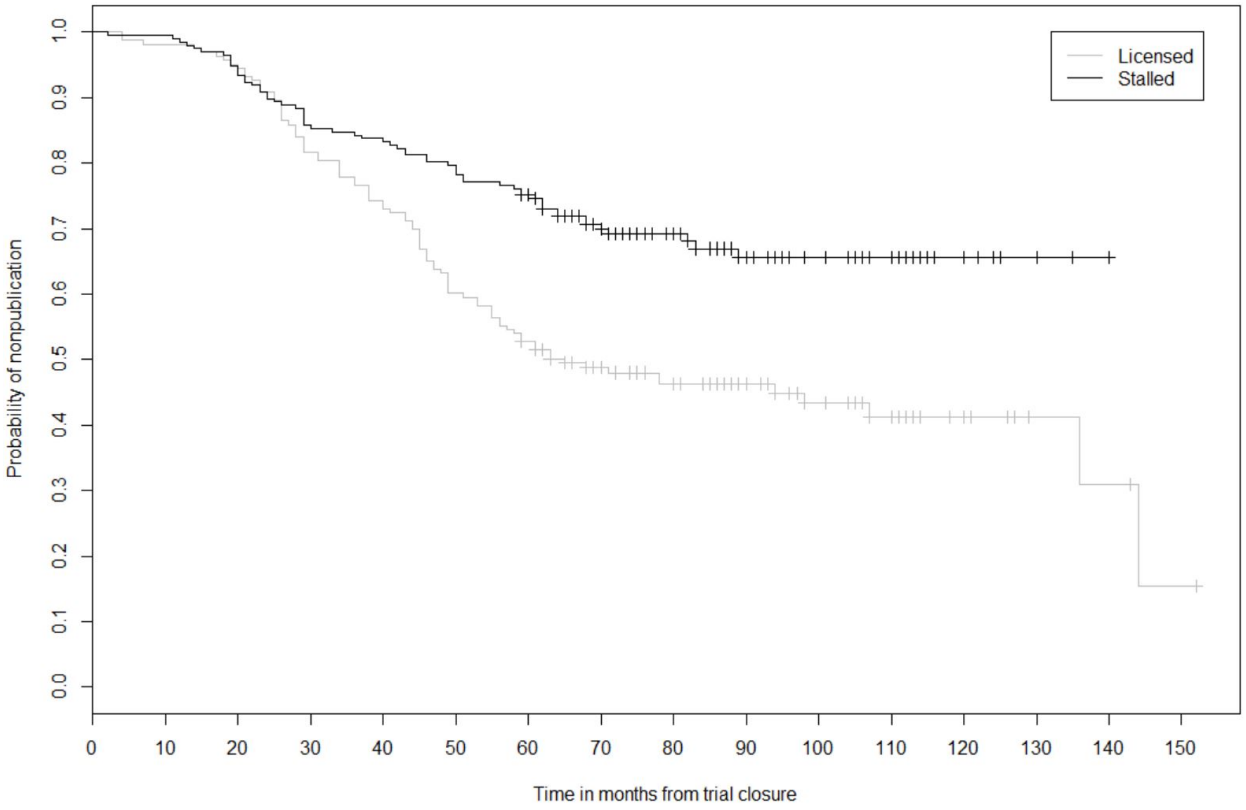

Figure 2: Kaplan-Meier survival estimate for time to nonpublication. Ticked lines represent censored values after which we have no follow-up data. The time to nonpublication curves are significantly different between cohorts (Log Rank Test: $X^2(1) = 16.8$, $p < 0.0001$ (N=360)).

Tables and table legends

Table 1: Drugs and trials included in our sample

	Licensed drugs (*n* = 8)	**Licensed drug trials (*n* = 163)**	**Stalled drugs (*n* = 28)**	**Stalled drug trials (*n* = 203)**
Alzheimer's disease				
			Bapineuzumab	2
			Bifeprunox	20
			Dimebon	24
			Lecozotan	8
			Neramexane	14
			Semagacestat	2
			Solanezumab	2
			Xaliproden	5
Epilepsy				
	Ezogabine	3	Brivaracetam	13
	Lacosamide	24	Carisbamate	14
	Perampanel	19		
Insomnia				
	Ramelteon	47	Almorexant	4
			Eplivanserin	7
			Esmirtazapine	10
			Indiplon	1
			Volinanserin	5
Migraine				
			Telcagepant	13
Multiple sclerosis				
	Fingolimod	15	Dirucotide	4
	Teriflunomide	5	Laquinimod	1

Parkinson's disease				
	Rasagiline	13	CEP-1347	1
	Rotigotine	37	Opicapone	20
			Pardoprunox	7
			Pitolisant	3
			Preladenant	5
			Sarizotan	5
			Tozadenant	1
Stroke				
			Desmoteplase	3
			NXY-059	3
			ONO-2506	6

Table 2: Flow of drug and trial selection		Licensed drugs	Stalled drugs
DRUGS Identification			
	Drugs identified through Drugs@FDA	16	0
	Drugs identified through CenterWatch	156	0
	Drugs identified through CT.gov	0	1837
Screening			
	Drugs after duplicates removed	160	720
	Drugs screened	160	720
	Drugs excluded	131	236
	Not indication of interest	68	0
	Not within timeframe	58	235
	Generics	5	0
	Phase III trial withdrawn	0	1
Eligibility			
	Drugs assessed in-depth for eligibility	29	484
	Drugs excluded	21	456
	Not NME approvals	14	0
	Old drugs	6	11
	Dietary supplement	1	37
	Licensed	0	179
	Not target indication	0	178
	Other	0	51
Included			
	Drugs included in creating the trial sample	**8**	**28**
TRIALS Identification			
	Trials identified through CT.gov	448	306
Screening			
	Trials after duplicates removed	448	306
	Trial screened	448	306
	Trials excluded	282	103
	Not within timeframe	279	102
	Withdrawn trial	2	1
	Observational	1	0
Eligibility			
	Trials assessed in-depth for eligibility	166	203
	Trials excluded	3	0
	Not drug of interest	2	0
	Expanded access trial	1	0
Included			
	Trials included in qualitative synthesis	**163**	**203**
	Trials included in quantitative synthesis	**163**	**203**

Table 3: Demographics of trial sample

		Licensed drug trials (n = 163)	Stalled drug trials (n = 203)
Indication			
	Alzheimer's	0 (0%)	77 (38%)
	Epilepsy	46 (28%)	27 (13%)
	Insomnia	47 (29%)	27 (13%)
	Migraine	0 (0%)	13 (6%)
	Multiple sclerosis	20 (12%)	5 (3%)
	Parkinson's	50 (31%)	42 (21%)
	Stroke	0 (0%)	12 (6%)
Phase			
	Not stated	5 (3%)	1 (1%)
	Phase I	15 (9%)	59 (29%)
	Phase I-II	0 (0%)	2 (1%)
	Phase II	50 (31%)	49 (24%)
	Phase II-III	7 (4%)	7 (3%)
	Phase III	66 (41%)	85 (42%)
	Phase IV	20 (12%)	0 (0%)
Sponsor			
	Industry only	138 (85%)	196 (97%)
	Other	25 (15%)	7 (3%)
Trial status			
	Completed	142 (87%)	172 (85%)
	Terminated	19 (12%)	28 (14%)
	Unknown	2 (1%)	3 (1%)
Trial type			
	Core	133 (82%)	183 (90%)
	Extension	30 (18%)	20 (10%)
Comparator type[a]			
	Placebo	104 (64%)	134 (66%)
	Active	26 (16%)	32 (16%)
	Combo	3 (2%)	17 (8%)
	None	44 (27%)	44 (22%)
	Not stated	2 (1%)	2 (1%)
Trial closure date[b]			
	Before sample median	83 (51%)	100 (49%)
	After sample median	80 (49%)	103 (51%)
Subject enrolment[c]			
	Total	38 513	57 970
	Mean	245.3	308.4
	Median	140	120
	Range	1–1272	4–3200
Trial duration (months)[b]			
	Mean	20.5	14.9
	Median	17	13
	Range	0–102	0–68

[a] Categories are not mutually exclusive: for example, a trial might figure in both "placebo" and "active" comparator categories.
[b] Data available for N=163 and N=197 licensed and unlicensed drug trials, respectively.
[c] Data available for N=157 and N=188 licensed and unlicensed drug trials, respectively.

Table 4: Proportions of published trials[a]

		Licensed drug trials (n = 163)	Stalled drug trials (n = 203)
Extent[b]			
	Full	91 (56%)	64 (32%)
	Abstract	12 (7%)	20 (10%)
	CT.gov	31 (19%)	25 (12%)
	Summary	13 (8%)	0 (0%)
	No public data	16 (10%)	94 (46%)
By indication			
	Alzheimer's		10/77 (13%)
	Epilepsy	23/46 (50%)	15/27 (56%)
	Insomnia	23/47 (49%)	5/27 (19%)
	Migraine		10/13 (77%)
	Multiple sclerosis	12/20 (60%)	2/5 (40%)
	Parkinson's	33/50 (66%)	16/42 (38%)
	Stroke		6/12 (50%)
By phase			
	Not stated	1/5 (20%)	0/1 (0%)
	Phase I	10/15 (67%)	13/59 (22%)
	Phase I–II		1/2 (50%)
	Phase II	21/50 (42%)	26/49 (53%)
	Phase II–III	4/7 (57%)	2/7 (29%)
	Phase III	45/66 (68%)	22/85 (26%)
	Phase IV	10/20 (50%)	
By sponsor			
	Industry only	81/138 (59%)	62/196 (32%)
	Other	10/25 (40%)	2/7 (29%)
By trial status			
	Completed	86/142 (61%)	61/172 (36%)
	Terminated	4/19 (21%)	2/28 (7%)
	Unknown	1/2 (50%)	1/3 (33%)
By trial type			
	Core	77/133 (58%)	64/183 (35%)
	Extension	14/30 (47%)	0/20 (0%)
By trial closure date			
	Before sample median	40/83 (48%)	22/101 (22%)
	After sample median	51/80 (64%)	42/102 (41%)
By comparator type			
	Placebo	62/104 (60%)	59/134 (44%)
	Active	10/26 (39%)	8/32 (25%)
	Combo	0/3 (0%)	2/17 (12%)
	None	23/44 (52%)	5/44 (11%)
	Unknown	1/2 (50%)	0/2 (0%)
Subject enrolment[c]			
	Total	24 293	24 724
	Mean	267.0	386.3
	Median	130.0	200.5
	Range	10–1272	10–3306

[a] Only full journal articles are considered publications for the subgroup analyses and for descriptions of enrolment.
[b] Levels of publication are hierarchical. Trials are counted only once at the highest level of result reporting.
[c] Data available for N=91 and N=64 full publications of licensed and unlicensed drug trials, respectively.