

BMJ Open Are large prospective trials on antidepressants in mental disorders seeding trials? A descriptive study of trials registered on ClinicalTrials.gov

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ABSTRACT

Objectives This descriptive study of registered trials aimed to identify large clinical trials on antidepressants for mental disorders: (1) to assess what proportion could be labelled as ‘seeding trials’ (trials for marketing purposes) and (2) to describe their methodological characteristics and outcomes.

Design A search was conducted across all trials registered on ClinicalTrials.gov by drug name in March 2017.

Setting All trials registered in the database of ClinicalTrials.gov were screened. Large registered studies were received and studies focusing prospectively on the effects of antidepressants in mental health disorders. Specific data items were extracted automatically, and subsequently inspected, corrected and completed by hand.

Participants Prospective studies were selected focusing on the effects of antidepressants in any mental health disorder with 800 participants or more planned for inclusion.

Main outcome measures Three members from the study team independently assessed the following ‘seeding trial’ characteristics in each registered study: a high level of involvement of the product manufacturer in the study design, in the data analysis and reporting of the study, an abnormally low ratio of patient numbers to study site, spin and/or omissions of clinically relevant findings in the abstracts, and conclusions that focused on secondary endpoints and surrogate markers. Secondary outcomes were the exploration of a functional outcome and suicidality.

Results 31 trials were identified from clinical trials database. 18/31 were published (58%). 8 of these 18 (44%) studies were identified as possible seeding trials. 13/31 (42%) large trials planned to explore functioning and 5/31 (16%) suicidality.

Conclusions Large trials are rare in the field of antidepressant research. Some could be ‘seeding trials’. Few explored suicidality. Identifying seeding trials from incomplete data entries in registries, especially when almost half of the studies were still unpublished, posed considerable challenges. The delay between our research and publication limits the strength of our conclusions.

PROSPERO registration number CRD42017065591.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ A search was conducted on ClinicalTrials.gov by drug name to identify large (ie, >800 patients) studies on antidepressants in mental health disorders.
- ⇒ Specific data items or relevant portions of text were extracted automatically from each record, and subsequently inspected, corrected and amended by hand.
- ⇒ Assessment of ‘seeding trial’ characteristics in each registered study.
- ⇒ Assessment of clinical outcomes in these studies.
- ⇒ Searches conducted 5 years ago weaken the strength of evidence.

BACKGROUND

Antidepressants are among the most prescribed treatments in the world and represent an important market for many drug companies. The 2019 Public Health England report showed that, between 2015–2016 and 2017–2018, the rate of prescribing for antidepressants increased from 15.8% of the adult population to 16.6%.¹ These treatments are therefore ‘naturally’ a subject of marketing practice. Of particular interest among the innumerable marketing strategies is the conduct of large clinical trials driven by commercial as opposed to scientific rationales, also known as ‘seeding trials’.²

Indeed, large trials can sometimes be hijacked for marketing purposes, because they allow product sampling to be targeted towards ‘key opinion leaders’ and practitioners, thus ensuring their commitment and loyalty to the product.³ For example, trials such as ADVANTAGE (a study conducted on arthritis)⁴ were thought to have been driven exclusively by marketing interests, and consequently to have represented a waste of funding, research efforts⁵ and patients’ time given that no new knowledge was produced. There is no gold standard to identify these

so-called ‘seeding’ trials. But despite poor consensus, it has been suggested⁶ that they tend to exhibit one or more of the following characteristics: a high level of involvement of the product manufacturer (1) in the study design, (2) in the data analysis and/or (3) in the reporting of the study; (4) a conspicuously low ratio of patient numbers to study sites that is abnormally and unjustifiably low for conditions that are relatively common and could therefore enable the recruitment of large numbers of patients from fewer sites; (5) ‘spin’ and/or omissions of clinically relevant findings in the abstracts reporting the trial results and (6) conclusions that focus on secondary endpoints and surrogate markers. For these reasons, large trials, planning to recruit large number of patients, are a particularly suitable target to marketing practices as they can reach many practitioners.

On the other hand, well-conducted large trials are paramount in antidepressant research. A simulation study⁷ suggested that 650 patients were needed for a two-arm trial to be adequately powered. And indeed, few trials reach this sample size, and therefore, most conducted lack the statistical power to show the expected effect. Most of these non-positive small trials are as yet unpublished.⁸ In addition, small trials are unlikely to detect any harmful events for patients, even those that are relatively common, let alone rare, life-threatening events. Despite hundreds of trials, the literature is still controversial and the clinical relevance of the small differences versus placebo observed in meta-analyses⁹ may be outweighed by harmful effects.^{10 11}

Conversely, because of their increased statistical power, large trials could answer questions about key patient-relevant outcomes such as suicidality and/or functioning. An international survey on patients, informal caregivers and healthcare professionals (N=3003) identified suicidality, mental pain and impaired functioning as priority areas of concern, and yet neither of these factors is included in more than one of the seven most widely used depression scales.¹² While major depressive disorder is a leading cause of disability, Cipriani *et al* noted in their meta-analysis of randomised controlled trials that evidence for functional outcomes was lacking. Large, well-designed trials could help to avoid these shortcomings and explore the patient relevant outcomes.

This descriptive study of large clinical trials on antidepressants for mental disorders registered on ClinicalTrials.gov, a federally funded, public database for registrations and results from clinical trials¹³ aimed (1) to identify potential seeding trials and (2) to describe main methodological characteristics of those trials, with a focus on patient-relevant outcomes (functionality and suicidality) that are expected to be assessed in large trials.

METHODS

We developed and followed a standard protocol (systematic review registration: PROSPERO 2017 CRD42017065591).

Searches

The screening for potentially relevant trials was conducted on all trials registered on ClinicalTrials.gov in March 2017 by one of the authors (DF). To ensure maximum accuracy and exhaustiveness, the entire database was downloaded; all searches and record retrievals and all data extractions were conducted directly on the database via a purposely written Java code.

A list of initially relevant records from ClinicalTrials.gov was compiled by selecting all records that included, anywhere in the text except in the description of the eligibility criteria, one or more of the following drug names: ‘bupropion’, ‘citalopram’, ‘duloxetine’, ‘escitalopram’, ‘fluoxetine’, ‘fluvoxamine’, ‘milnacipran’, ‘mirtazapine’, ‘paroxetine’, ‘reboxetine’, ‘sertraline’, ‘venlafaxine’, ‘agomelatine’, ‘vortioxetine’. We focused on ‘new-generation antidepressants’ and did not include older compounds such as imipramine antidepressants. The part of the text describing the eligibility criteria was removed from the searches because the drug names in this part of the text were most frequently associated with the trial exclusion criteria or with the description of other factors that would have increased the rate of false positives in the search.

From the initial list of potentially relevant titles, a subset of the larger-sized trials was selected for analysis. We selected large trials defined as trials with 800 participants or more planned for inclusion, in accordance with a previous publication.¹⁴

One reviewer (SM) reviewed the list of large registered studies and selected studies focusing prospectively on the effects of antidepressants in mental health disorders (excluding tobacco addiction). A second reviewer (FN) double-checked the output from this selection. A third reviewer (I-AC) was involved in helping to reach a consensus between the other two reviewers when necessary. Whenever two records appeared to correspond to the same trial, the corresponding authors were contacted to clarify the identity of the records.

Data extraction

Specific data items or relevant portions of text were extracted automatically from each record, and subsequently inspected, corrected and completed by hand (SM). All publications connected to the clinical trial registration were either taken from ClinicalTrials.gov or, if none was found, from a search on PubMed using the trial registration number or the trial title. In case of missing data, the corresponding authors listed in the trial registration were contacted by email.

For each trial, the following characteristics were collected: mental disorder reported on the registration, preregistration of a suicide risk outcome (with the measurement instrument and the timeline), preregistration of a functional outcome (with the measurement instrument and the timeline), study phase, type of study (efficacy/safety/physiopathology), use of a comparative design, use of a randomised design, number of arms,

duration, planned sample size, sample size reached at the end of study, number of inclusion criteria, number of exclusion criteria, population (adults/children/both), exclusion of patients with suicidal ideations, sponsorship, number of investigators (absolute and relative to sample size), final status, time to completion (absolute, per size), publication status and number of publications, and finally reporting of the 'suicide risk' and/or 'function' outcome domains in the published results with the corresponding outcome measures (which could potentially differ from one study to another).

Primary outcome: identification of market-driven trials

Three members of the study team (SM, FN and I-AC) independently assessed all study registrations and the corresponding published papers (all manuscripts including their abstracts, contributions, funding and acknowledgement sections), and rated all included trials on the characteristics for market-driven trials described above: high level of involvement of the product manufacturer in study design (1) in the data analysis, (2) and in the reporting of the study, (3) ratio of numbers of patients to study site, (4) spin and (5) (defined as the 'use of specific reporting strategies, for whatever motive, to highlight that the experimental treatment is beneficial despite a statistically non-significant difference for the primary outcome, or to distract the reader from statistically non-significant results')¹⁵ and omissions of clinically relevant findings in abstracts, and conclusions that focused on secondary end-points and surrogate markers (6). The researchers followed the method described by Barbour *et al*⁶ to conduct their assessment and as Barbour *et al* 'they did not use fixed criteria, but based their decisions on the extent to which they each felt the six characteristics of marketing influenced trials described above influenced the research reported'. For each trial, a consensus decision was reached through discussion to identify studies that were thought to be suspected marketing trials.

Secondary outcomes

For each trial, we examined whether suicide or functioning were used as outcomes. For this purpose, we noted whether there was a preregistration of a suicide risk outcome (with its definition and the assessment tool used), preregistration of a functional outcome (with its definition and the assessment tool used), the study phase, the type of study (efficacy/safety/physiopathology) and reporting of suicide risk and functional outcomes in the findings of published reports. We also noted all study characteristics described in the data extraction paragraph.

Analysis

A descriptive analysis of each of the parameters described above was carried out. Trial characteristics were also described and discussed in qualitative terms, especially for the studies thought to be suspected marketing trials.

Patient and public involvement

We had no established contacts with specific patient groups who might be involved in this project. No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results, nor will we disseminate results directly to patients.

RESULTS

The algorithm identified 1999 trials registered up to March 2017 (flow chart). Among them, 42 mentioned no sample size, and 1855 had fewer than 800 participants. Out of the remaining 102 registered trials, 37 did not relate to a mental disorder, 20 did not include antidepressants and 6 were not prospectively registered. Full registration details of the 39 remaining studies were scrutinised and 8 registered trials were excluded. For two of these, a closer examination of the registered studies showed that the preplanned sample sizes were under 800. Another five (2+3) were duplicate registrations (3 registrations referenced the same study and four were different registrations derived from the same cohort), and finally another registration was for a meta-analysis.

Therefore, 31 large prospective registered trials on antidepressants for the treatment of mental disorders were included. Out of these, 18/31 were published in 228 papers (1 was published in 119 papers, 1 in 57, 1 in 17, 1 in 5 and the other in fewer than five papers, with a median number of publications of 3 per registered trial with at least one publication). For one study, only the protocol was published. This process, and the registered trials, are described in [figure 1](#) and online supplemental e-Table 1. Data extraction was performed in August 2018.

Trial characteristics

The types of registered trials are described in online supplemental e-Table 1. The characteristics of comparative, randomised, double-blind studies are described in online supplemental e-Table 2. The study phase was included on ClinicalTrials.gov for 22 of the 31 registered trials. Ten registered trials of 31 were labelled phase III studies, 11/31 were labelled phase IV and 1 was incorrectly labelled phase I (this trial explored a pharmacogenetic hypothesis). Of 31, 18 studies were comparative, including 15 randomised controlled trials (7 were double-blind). Thirteen registered trials had a single arm, nine had two arms, four had three arms, two had four arms, one had five arms and two large studies, STEP-BD (NCT00012558) and STAR*D (NCT00021528), were conducted in several stages and the number of arms depended on the stage concerned. The median duration of study follow-up was 16 weeks (range: 0.14–522). The shortest lasted 1 day and the longest 10 years. Three out of 18 published studies analysed fewer than 800 patients. The median sample size enrolled in completed or non-recruiting studies was 1039 (range: 807–4360).

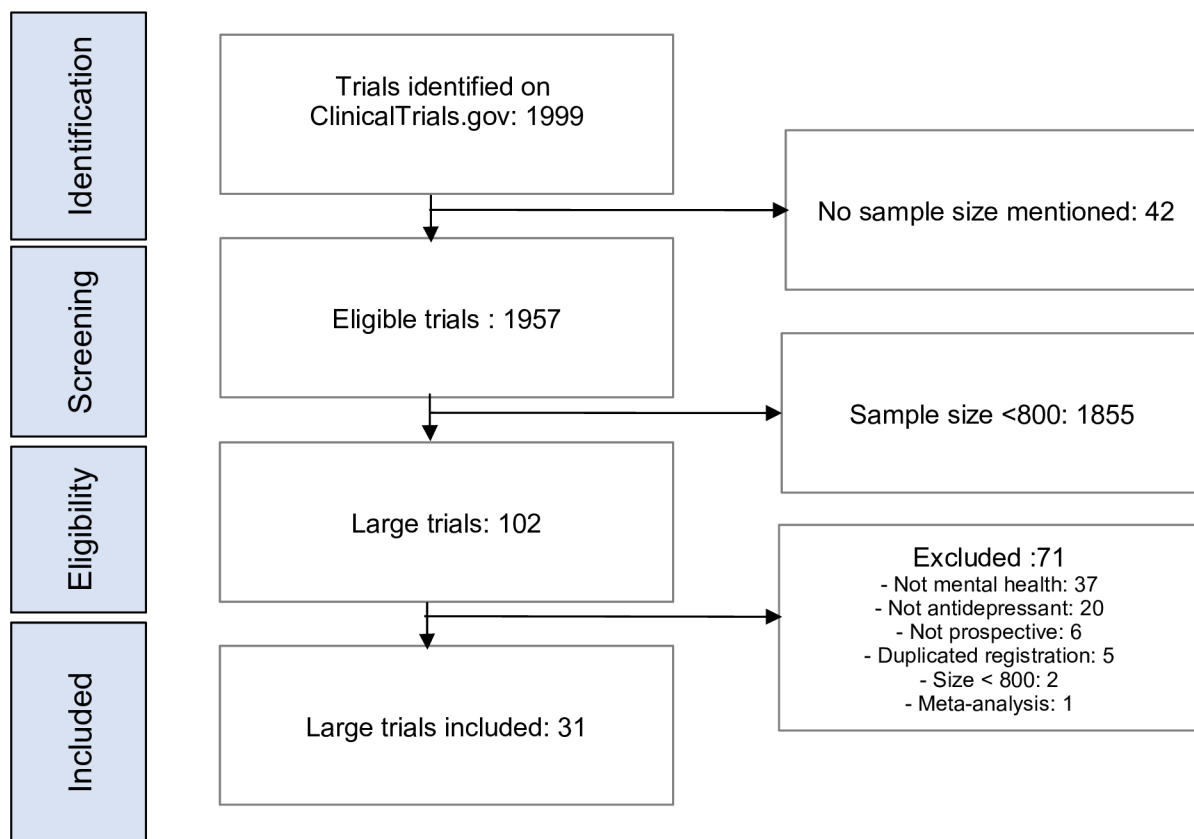


Figure 1 Study flow chart.

Twenty-four studies included an adult population, five included adults and children and two only included children. In 15 studies, patients with suicidal ideation were excluded. Twenty-one studies were sponsored by the pharmaceutical industry, seven studies were sponsored by a public institute and three studies were sponsored by a medical centre. The number of investigators ranged from 1 to 836. This wide variability suggests that the information was often inaccurate in study registrations with possible confusion between investigators and centres. For 17 of 18 studies published, we were able to complete this information from the paper (the other paper being in Japanese). In addition, 2 registrations of 31 did not provide the number of investigators on ClinicalTrials.gov and this information could not be retrieved because these studies were still unpublished. The computed ratio of patients to investigators ranged from 4.2 to 1080 and was extremely variable. This ratio should be interpreted with caution due to poor reporting on ClinicalTrials.gov. Four studies were recruiting at the time of the search, 23 were completed and 4 were still active but not recruiting. Seventeen registered trials had published results. Among the 23 completed studies, results from 14 studies were published; in 1 of these 14 studies, only preliminary results were published. Out of the eight ongoing studies, three had published some material (preliminary results, description of participant characteristics), and only one study had a protocol publication.

Identification and characteristics of market-driven trials

Agreement between reviewers was good in terms of extracting data on high levels of involvement of the product manufacturer in the trial design (1 disagreement/17 trials), data analysis (0 disagreement/17 trials) and reporting of the study (0 disagreement/17 trials) and the ratio of patient numbers to study site for conditions that are relatively common (0 disagreement/17 trials). Data extraction, however, required further consensus for the evaluation of spin (6 disagreements/17 trials) and conclusions (agreements 3/17 trials) and needed further discussion to reach a consensus. Our assessment of published trials, after the final consensus, is presented in figure 2. Eight trials of 17 were thought to have the features of suspected marketing trials. The characteristics of these eight trials are detailed in online supplemental e-Table 3. Of 17 trials, 5 of these trials were randomised controlled trials, 4 of which were double-blind. Three were non-comparative trials. Six of these were phase IV studies, and two were phase III. The trial duration ranged from 1 day to 1 year. Five trials prescribed venlafaxine, two duloxetine and one escitalopram. Sponsorship for these eight trials came from three companies: Pfizer, Wyeth and Eli Lilly. Only adult participants were included. None of the presumed seeding trials explored suicidality (four excluded suicidal patients) and five of them had a prespecified functional outcome. The sample size ranged from 840 to 3543, and the number of patients analysed

Conclusions focused on secondary end-points and surrogate markers	No	No	?	Yes	No	Yes	No	Yes	Yes	No	No	No	No	?	Yes	Yes	?
Spin and omissions of clinically relevant findings in abstracts	No	No	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	?	Yes	No	?
Abnormally low ratio of numbers of patients to study site	No	No	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No
High level of involvement of the product manufacturer in reporting of the study	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	No	?
High level of involvement of the product manufacturer in data analysis	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	No	?
High level of involvement of the product manufacturer in study design	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No
	NCT00012568	NCT00021528	NCT00046020	NCT00479726	NCT00494377	NCT00613470	NCT00693849	NCT00788944	NCT00810069	NCT0087224	NCT01106693	NCT01309542	NCT01352559	NCT01421342	NCT01432457	NCT02023567	NCT02388343

Figure 2 Seeding trial characteristics (yes/no) for all published trials.

ranged from 566 to 3431. In many cases, there were significant differences between the number of patients planned and the number actually included, and some trials enrolled more patients than originally planned. For instance, trial NCT00810069 planned 580 but enrolled 840 patients, and trial NCT00788944 planned 865 patients but enrolled 970. Of these eight trials, one did not reach its target sample size: trial NCT00479726 planned 8000 but enrolled only 3543 patients. Regarding the published reports describing the main findings of these studies, 7/8 mentioned ‘medical writing support’. All but 1 of the 59 different authors of these publications had a conflict of interest linked to the company sponsoring the trial: 34/59 were company employees and 24 of the 25 remaining authors received payments or research funds from the company. Among authors who were company employees, one was involved in three of these papers and two were involved in two of these papers. Among the authors with links to the company, one was involved in two papers. We found spin and omissions in the abstract of all eight potential seeding trials, and found that four trials concluded on secondary endpoints and surrogate markers. Among these eight suspected trials, six were published in the *Journal of Clinical Psychiatry* (four) or in two of its affiliate journals, the *Primary Care Companion of the Journal of Clinical Psychiatry* (one) and the ‘*Primary Care Companion CNS Disorders*’ (one). The other two were published in the *Journal of Clinical Psychopharmacology* and the *Journal of Affective Disorders*.

Outcomes measured

Suicidality

Suicide risk was prespecified as an outcome in 5 out of 31 registered trials. The characteristics of the five registered trials including a prior choice of suicidality as an outcome are shown in figure 3A and online supplemental e-Table 4. The definitions and measurement tools varied. Three studies considered suicide risk as a primary outcome. Out of the five registered studies, two were comparative (one was randomised). Two studies included children only, one both children and adults and the other two adults only.

Two concerned sertraline, one agomelatine, one vortioxetine and one bupropion. Two were completed (one unpublished without results and one unpublished with

results posted on ClinicalTrials.gov), one had an ‘active, non-recruiting’ status (its preliminary results were published in three papers, but none thus far had included a suicide risk outcome), and two were still ongoing.

Measurement tools used in these studies are presented in figure 3B.

Functioning

Thirteen registered trials prespecified the use of functional outcomes (in all cases as secondary outcomes) of 31. The characteristics of these 13 registered trials are shown in figure 3C and online supplemental e-Table 5: 8 were comparative and randomised. Results from 7 of these 13 studies were published (with 6 reporting results on the functional outcome) and 6 were unpublished (3 were ongoing).

There was some heterogeneity across studies in terms of the tools used (figure 3D). The most common endpoints were scores on the Sheehan Disability Scale and the Short Form Health Survey (both were found in five studies). Quality of Life Enjoyment and Satisfaction was used in four studies. The Work and Social Adjustment Scale, the Euro Quality of Life Scale and the Work Productivity and Activity Impairment Questionnaire were used in two studies. Other measures were only present once.

DISCUSSION

Statement of principal findings

Large antidepressant trials are rare among studies registered on ClinicalTrials.gov. Indeed, 31 registered trials with planned sample sizes of over 800 were found, out of which only 7 were randomised, double-blind, comparative trials. A small proportion of these trials (5/31) explored suicidality, whereas almost half (15/31) excluded potentially suicidal patients. Functional outcomes were slightly better represented (13/31). Of the 31 registered trials identified, only 18 were published, and 17 reported results, giving a proportion of 40% of unpublished trials that similar to previous publications.¹⁶ From these 18 published trials, we applied Barbour *et al*’s criteria for 17 (1 written in Japanese, could not be rated), and we were finally able to identify 8 trials as possible seeding trials, which amounted to a proportion of 47% (8/17). Some

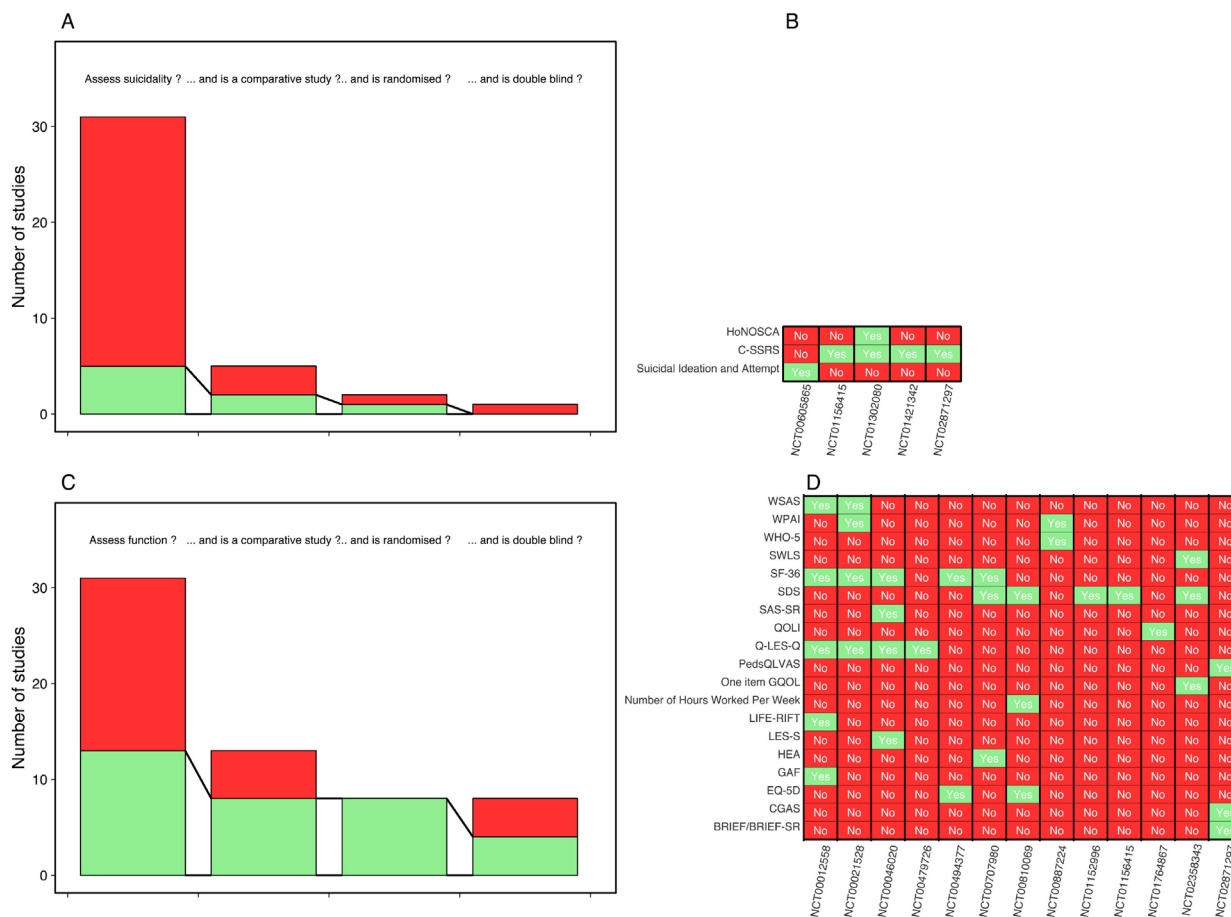


Figure 3 Study design, publication status and scales used for studies measuring suicidality and functioning. (A) Suicidality: study design and publication status (green=published/red=unpublished). (B) Suicidality: scales used in all registered trials. (C) Functioning: study design and publication status (green=published/red=unpublished). (D) Functioning: scales used in all registered trials. BRIEF/BRIEF-SR, Behaviour Rating Inventory of Executive Function/ BRIEF self-report version; CGAS, Children Global Assessment Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; EQ-5D, Euro Quality of Life scales; GAF, Global Assessment of Functioning; HEA, Health Economic Assessment Questionnaire; HoNOSCA, Health of the Nation Outcome Scales for Children and Adolescents; LES-S:Life Enjoyment Scale Short Version; LIFE-RIFT:Life Range of Impairment Functioning Tool; Number of Work Hours Missed in the Last 4 Weeks, number of hours worked per week, number of hours missed in the last 4 weeks, numbers of work hours missed due to depression in the last 4 weeks; Numbers of Hours Worked Per Week, Number of Hours Worked Per Week; One-item GQOL, One-item Global Quality of Life scale; PedsQLVAS, Paediatric Quality of Life Inventory Present Functioning Visual Analogue Scales; Q-LES-Q, Quality of Life Enjoyment and Satisfaction; QOLI, Quality of life Inventory; SAS-SR:Social Adjustment Scale Self Report; SDS, Seehan Disability Scale; SF-36, Short-Form Health Survey; SWLS, Satisfaction With Life Scale; WHO-5, WHO Five Well-Being Index; WPAI, Work Productivity and Activity Impairment; WSAS, Work and Social Adjustment Scale.

of the remaining 13 unpublished trials may have been seeding trials, but we could not rate them due to incompletely reported data. For these trials, the only applicable criterion was the ratio of numbers of patients to study site and 4/13 had a ratio <10.

For instance, a trial called ‘Drug Use Investigation for PAXIL Tablet’ was identified (NCT01371435). This trial was carried out from March 2001 to December 2003; it included 3708 participants and was open-label, non-comparative, non-controlled, multicentre and post-marketing surveillance. The objective was to detect adverse events, and the study planned to enrol 3000 patients from 500 centres with an investigator/patient ratio of 6. We did not have enough data to assess this trial in depth, as results were published in three articles

in Japanese—which we could not examine in detail. Another similar preregistered trial was found, named: Special Drug Use Investigation for PAXIL Tablet (Investigation in Case of Administered From 20 mg/Day) and registered as NCT01371474. This trial was conducted between March 2006 and February 2007, and had an identical design and outcome, and planned the same ratio patient/investigator, but included fewer participants and was still unpublished. Non-interventional postmarketing studies seem suspicious especially since it has been shown that participating physicians prescribe more of the investigated drug.¹⁷ It is worth noting that the PAXIL (paroxetine) study 329 is a well-described example of mismatches between marketing claims made in the study and the data shown in an independent reanalysis.¹⁸ There were also

major documented breaches in scientific integrity for paroxetine, including a ghost management programme ironically called CASSPER (Case Study for Peer Review).¹⁹ Lastly, two of these large trials were published in over 50 papers, while for the vast majority (and indeed, all those that were rated as being potential marketing trials), the number of publications did not exceed 5.

Findings in relation to other studies

Little is known about the exact proportion of marketing trials. Barbour *et al* found a prevalence of 21% (95% CI 15% to 27%) of potential marketing trials among randomised controlled trials published in six general medical journals in 2011.⁴⁻⁶ A higher proportion was found in the present survey (8/17) with considerable uncertainty due to missing data. This difference could be explained by differences in study selection. The studies evaluated by Barbour *et al*⁶ had been published in prominent medical journals, where papers generally undergo more stringent peer-reviews, thus possibly leading to an underestimation of the actual prevalence of suspected marketing trials.²⁰ Certain features of marketing trials, such as the relative triviality of the research question,²⁻²¹ could also hamper chances of publication in such journals. In addition, our sample included all types of trials regardless of design, and some characteristics 'naturally' raise suspicions, particularly in non-comparative trials. Conversely, we may have overestimated the proportion of suspected marketing trials by focusing only on large trials, as these may be better aligned with the marketing objective of reaching a large number of physicians as a result of their aim for broad recruitment/dissemination. In addition, two features of psychopharmacology could have contributed to the high proportion of seeding trials observed: there has been little innovation in the field of psychotropic drug development²² and this field of research concerns chronic conditions that could be seen as privileged marketing targets. Little is known about the impact of marketing trials, but it has been suggested that differences in prescriptions across countries could be linked to promotional strategies, using marketing trials in particular.²³

Limitations of this study

Our descriptive study has several limitations. First, we underestimated the time required for extraction and manual verification. Searches conducted 5 years ago weaken the strength of evidence. Our work, started in March 2017, could not be completed until 2018 and submitted in 2020 and we did not have the resources to update our searches. Second, we used a pre-existing definition of large trials in line with Contopoulos-Ioannidis *et al*¹⁴ and, similarly to these authors, we should acknowledge that the definition of 'large' trial is unavoidably arbitrary.

Additionally, it is true that clinical trials with smaller sample sizes can have marketing goals. However, our focus was on 'seeding trials' that would hide marketing

aims under the guise of important research questions, such as phase IV, comparative effectiveness or monitoring of safety aspects that could not be assessed in pivotal phase III trials. Consequently, planning for large samples is a useful proxy to identify such seeding trials, particularly since large trials allow reaching a very large number of practitioners, which is another desirable marketing goal.

Overall, it was difficult to ascertain whether trials were marketing trials. Many features of suspected marketing trials have been described in several publications,²⁻⁴⁻⁶ but there is currently no consensus on their definition. The characteristics of suspected marketing trials are often difficult to identify and could depend on the subjectivity of the investigator. We tried to limit this bias by involving three independent reviewers and we used criteria derived from a previous publication (online supplemental e-Table 6).⁶ In the literature, few seeding trials^{5,24} have really been documented, and in the absence of internal documents, 'marketing' is impossible to prove. Published studies can misconstrue and hide sponsor involvement, and it is, therefore, likely that the actual number of seeding trials is underestimated.

Two criteria are, however, objective: the number of recruiting centres and the number of patients recruited by each centre.⁶ The presence of a large number of centres enrolling few patients is indeed suspicious because this recruitment strategy appears as expensive and unreliable: (1) it requires a large number of recruiting centres (it is therefore more expensive), (2) it requires complex coordination and infrastructures and (3) it could result in a loss of data quality. However, these arguments may not hold, as they could also allow for a more rapid recruitment of study participants, spread across a wider area and also including smaller centres with fewer resources and limited recruitment possibilities. In addition, reporting on ClinicalTrials.gov was poor, which made it difficult to ascertain information in this survey. In some instances, registered data diverged from the publications and it was sometimes difficult to clarify whether these discrepancies were due to misreporting in the publication or to registration errors on ClinicalTrials.gov. In addition, data for a large number of studies were incomplete. Third, our study only included trials recorded on ClinicalTrials.gov. Although ClinicalTrials.gov is the most comprehensive registry, it is possible that we missed trials registered on other registries or conducted before registration was made mandatory by the ICMJE in 2005. However, this will be less likely in the future because the regulatory authorities are now increasingly demanding more transparency, even for result postings. For example in the USA, the National Institute of Health (NIH) with the 'final rule' requires all NIH-funded clinical trials to report their data on ClinicalTrials.gov.¹³ In addition, our search could have overlooked records where (1) the name of antidepressants was not explicitly stated



or recorded with errors and (2) the planned sample size was lacking or erroneous.

Conclusion

Large trials are rare in the field of antidepressant research. In the few existing trials, key outcomes such as suicidality and the functional impact of mental disorders were little studied. A significant proportion of these trials could be marketing trials ('seeding trials'). While marketing trials are difficult to spot, the quality of the literature could be improved by the development of an acknowledged and consensual set of patient-centred outcomes²⁵ along with guidelines providing details on how these outcomes should be assessed in adequately powered studies. These simple interventions could help to ensure that large trials explore the most informative outcomes, enabling the field to make faster progress and to maximise the value of clinical trial data. Further to this, health authorities and institutional review boards should require better transparency for large trials and should advise on setting research priorities, enabling studies to be designed and evaluated in the context of a broader research agenda in the field. Last, we recommend that medical journals publishing industry sponsored research systematically screen seeding trials characteristics and make this assessment transparent with the published paper in case such trials are published.

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Contributors SM, I-AC, DF, AC and FN developed the protocol, SM, I-AC and FN performed data extraction and coding, SM wrote the first draft of the manuscript. I-AC, DF, AC and FN reviewed the manuscript critically. All authors have read and approved the manuscript. SM accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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