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FACULTY OF HEALTH AND MEDICAL SCIENCES

PhD Thesis

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Effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on suicidality, violence, and quality of life.

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Title / Subtitle:	Effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on suicidality, violence, and quality of life.
Subject description:	This PhD thesis explores the benefit of using clinical study reports compared to published journal articles to assess the risk of suicidality, violent behaviour and other relevant harms of SSRIs and SNRIs and are their impact on the quality of life of people on these medications.

Principal supervisor: Peter C. Gøtzsche
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Preface

The thesis is structured according to the guidelines of the Graduate School of Health and Medical Sciences at the University of Copenhagen. The work on which this thesis is based was conducted at the Nordic Cochrane Centre and was funded by a research grant from the Laura and John Arnold Foundation. The principal supervisor was Peter C Gøtzsche, the co-supervisor was David Healy and the external assessor was Jørn Wetterslev.

This thesis is built on the following four papers:

- Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ* 2016; 352:i65.
- SharmaT, Gøtzsche PC, Kuss O. The Yusuf-Peto method was not a robust method for meta-anlayses of rare events data from antidepressant trials. *Journal of Clinical Epidemiology*, 2017 Nov;91:129-136.
- Sharma T, Guski LS, Freund N, Meng DD, Gøtzsche PC. Drop-outs rates in placebo-controlled trials of antidepressant drugs: systematic review and meta-analysis based on clinical study reports. ***(Submitted).***
- Sharma T, Rasmussen K, Paludan-Müller A, Gøtzsche PC. Selective reporting of SF-36 and EQ-5D health related quality of life outcomes in clinical study reports and publications of antidepressant trials. ***(Draft Manuscript).***

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PhD Thesis Summaries

English Summary

Clinical professionals and patients need to make decisions on the use of medicines based on the comparative assessments of their benefits and harms. Clinical professionals are guided by the conclusions of regulatory authorities and the published literature available to them. However, not all clinical trials are published and those that are, suffer from selective reporting. This problem of dissemination bias distorts the true effectiveness of drugs, exaggerating the benefits and minimising the harms. Trials of the antidepressants are notorious for gross dissemination bias and therefore the true effect of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are yet to be determined in a reliable manner.

This aim of this PhD was to shed light on true effects of SSRIs and SNRIs especially relating to suicidality, aggressive behaviour and quality of life by a series of systematic reviews using clinical study reports (CSRs), instead of journal publications as source documents. This has been accomplished by four research projects and related publications. The first was a systematic review and meta-analysis studying the serious harms of deaths, suicidality, aggressive behaviour and akathisia. The second was a methodological study considering the different statistical approaches for meta-analysing these rare outcomes in order to get more reliable and less-biased estimates for the effects of these serious harms. The third study compared the study drop-out rates and the fourth study looked at the quality of life outcomes using SF-36 and EQ-5D in the trials of SSRIs and SNRIs.

The results of the research show that there is substantial selective reporting that also occurs within CSRs and often details of serious harms were only available in individual patient listings or patients narratives. Using CSRs we found that suicidality and aggression more than doubled in children and adolescents that were on SSRIs or SNRIs compared to those on placebo. Through our second paper we found that this was most likely an underestimate and using a more reliable method such as beta-binomial, it is likely that the odds are two and a half and three times, respectively. Our research also showed for the first time that more patients on SSRIs or SNRIs dropped out from the trials when compared to patients on placebo. Our results also showed that quality of life outcomes are almost

never reported on in journal publications and their results can also be completely omitted from CSRs or have only very limited partial information noted.

In conclusions, due to problems of dissemination bias and problems of selective reporting even within CSRs, only raw data from clinical trials should be used for conducting systematic reviews. Accessibility to this data should be made available to the public by authorities such that researchers can independently confirm or refute regulatory decisions, in order to protect patient safety. As SSRIs and SNRIs can have very serious detrimental effects on children and adolescents, far more than previously noted, their use in young people should be reconsidered.

Danish Summary

Klinikere og patienter har behov for at kunne tage beslutninger om brug af forskellige typer medicin baseret på sammenlignende vurderinger af deres gavnlige og skadelige virkninger. Klinikere støtter sig til anbefalingerne fra sundhedsmyndighederne og i den lægevidenskabelige litteratur. Ikke alle kliniske forsøg bliver imidlertid publiceret og de som bliver, lider under selektiv afrapportering. Dette problem med formidlingsbias forvrænger den sande effekt af medicinen, overdriver effekten og minimerer skaderne. Forsøg med antidepressiva er berygtede for denne formidlingsbias, og derfor er den sande effekt af 'selektive serotonin genoptagshæmmere' (SSRI) og 'serotonin-noradrenalin genoptagshæmmere' (SNRI) ikke kendt.

Formålet med denne ph.d. var at belyse de sande effekter af SSRI og SNRI, specielt i forhold til selvmordsadfærd, voldelig opførsel og livskvalitet ('health related quality of life') i en række systematisk oversigtsartikler baseret på kliniske forsøgsrapporter (clinical study reports – CSRs) i stedet for publicerede sundhedsvidenskabelige artikler. Dette er blevet gjort i fire forskningsprojekter med tilhørende publikationer. Det første var en systematisk oversigtsartikel og meta-analyse, der undersøgte alvorlige skadevirkninger i form af dødsfald, selvmordsadfærd, voldelig opførsel, og akathisi (en ekstrem form for rastløshed, der er kendt for at øge risikoen for selvmord og mord). Det andet var et metodisk studie omhandlende de forskellige statistiske tilgange til at meta-analysere disse sjældne udfald for at få mere pålidelige estimater af effekterne af disse alvorlige skadevrkninger. Den tredje oversigt sammenlignede forsøgenes drop-out rater, og den fjerde oversigt så nærmere på livskvalitet, målt som SF-36 og EQ-5D, i forsøgene med SSRI og SNRI.

Resultaterne af disse undersøgelser viser, at der er en betydelig selektiv afrapportering, som også sker indenfor de kliniske forsøgsrapporter, og ofte er detaljer om alvorlige skadevirkninger kun tilgængelige i individuelle patientoptegnelser eller patienthistorier. Ved at bruge de kliniske forsøgsrapporter fandt vi ud af, at selvmordsadfærd og voldelig opførsel blev mere end fordoblet hos børn og unge, som fik SSRI eller SNRI, sammenlignet med dem, som fik placebo. I vores anden undersøgelse fandt vi ud af, at dette højst sandsynlig var en undervurdering og ved hjælp af mere pålidelige metoder, såsom beta-binomial metoden, blev det sandsynliggjort, at oddsene er

henholdsvis to en halv og tre gange så store for en skadelig effekt. Vores undersøgelser har også for første gang vist, at flere patienter som fik SSRI og SNRI, droppede ud af forsøgene sammenlignet med patienter, som fik placebo. Vores resultater har også vist, at livskvaliteten stort set aldrig bliver afrapporteret i videnskabelige publikationer, og at resultaterne kan også blive fuldstændig udeladt fra kliniske forsøgsrapporter eller kun blive delvist rapporeret.

Jeg konkluderer, at på grund af problemer med fomidlingsbias og problemer med selektiv afrapportering, selv inden for de kliniske forsøgsrapporter, bør det være rå-data fra kliniske forsøg, der bruges til at lave systematiske oversigtsartikler. Tilgængelighed til disse data for offentligheden bør sikres af offentlige myndigheder, således at forskere uafhængigt kan be- eller afkræfte de regulerende sundhedsmyndigheders beslutninger af hensyn til patienternes sikkerhed. Eftersom SSRI og SNRI kan have meget alvorlige skadevirkninger på børn og unge, meget mere end tidligere beskrevet, burde brugen af disse præparater til børn og unge genovervejes.

1 Introduction

Medicines and medical treatment have been around, in some form or the other, as long as mankind has, but the concept of assessing its quality has evolved gradually over time. The first Pharmacopoeias or the official books of drug quality standards, started to first appear in Europe from the 16th century[1] and in the United States of America (USA) in the 1800s, with their first government body to access the quality of medicines: the Bureau of Chemistry (the pre predecessor of the current Food and Drug Administration, FDA) also established.[2] More modern regulation of medicines only started to flourish after the Second World War[1] and the catastrophic deaths of over 100 people due to diethylene glycol poisoning following the use of a sulfanilamide elixir in 1937 facilitated the introduction of The Federal Food, Drug and Cosmetic Act with the premarket notification requirement for new drugs in USA from 1938. In the United Kingdom (UK), the National Health Service was formed after the war to provide effective treatment for free for the people and therefore what was 'effective' needed to be unpicked. Their Medical Research Council was tasked to understand this by funding research that considered appropriate scientific experimentation, which gave rise to the birth of the randomized controlled trial (RCT) that minimised the biases found within the observational design.[3,4] The first RCT on streptomycin for the treatment of tuberculosis was published in 1948 and paved the way for the new 'RCT-era'.[5]

It also brought along with it important ethical debates and discussions, that had till then evaded the literature, around treating patients with interventions with unknown effectiveness.[6] Archie Cochrane, a British Epidemiologist proposed that as resources would always be limited, they should be used to provide care equitably but only with those which had been shown in properly designed evaluations, to be effective. Despite there now being a rise of new RCT research, this was not always applied in a systematic manner for regulatory decisions. The second medical disaster of thalidomide (a sedative and hypnotic, which first went to market in 1956), fuelled and propelled this movement forward.[1-2] Between 1958 and 1960 thalidomide was introduced in 46 different countries and resulted in an estimated 10,000 babies being born with phocomelia and other severe deformities. The whole regulatory environment in the UK was transformed and a Committee on the Safety of Drugs was established in 1963 followed by a voluntary adverse drug reaction reporting system (Yellow Card Scheme) in 1964[1] that continues till this day.

These changes led to the routine use of the latest RCT evidence to support decisions of medical treatment; however there was no consistent overview of the fast growing medical literature. This changed with the establishment of an international collaboration to develop the 'Oxford Database of Perinatal Trials', funded by the World Health Organization and UK's Department of Health as a response to Archie Cochrane's criticism that there was no organised critical summary of the results of RCTs.[8] The systematic review method (a review that collates all relevant evidence in a systematic and explicit manner for a clearly defined research question) was formalised with the first Cochrane Centre in UK in 1992,[8] which ushered in a new era of evidence-based medicine (EBM)[9-11] which utilised knowledge from the fields of clinical epidemiology and statistics for the development of evidence-based guidance.[12]

Though this evolution towards EBM as a mechanism to determine effectiveness of medicines has been a positive one, in recent years it has been demonstrated that relying solely on published literature for undertaking systematic reviews gives a biased perception of the interventions' true effect. The benefits are overestimated and the harms are underestimated, mainly due to problems of dissemination bias.[13-17] History has also demonstrated that a specific disaster has kick started change in regulatory procedures and that they need constant renewal to ensure they are fit for purpose. We hope that another big disaster is not needed for regulatory agencies to open up their data and improve their data sharing and transparency policies, such that they are adequate to meet the needs of independent researchers and the public.

This thesis focuses on the issue of dissemination bias (summarised in section 1.1) in the case of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) trials as an example where this is exceptionally poor; (summarised in section 1.2).

1.1 Dissemination Bias

Systematic reviews are for the most part based on publically available data obtained from clinical trials in the form of published journal articles. We know however, that all trials conducted are not registered, and that only a fraction of trials registered are then subsequently published (publication bias), and those that are published are selectively reported on.[17-21] The extent of selective reporting

is exceptionally worse when the new drug does not show added benefit or shows a negative effect or where there are considerable adverse events.[18-22]

Clinical study reports (CSRs) are detailed summaries of trial results prepared by the drug industry for submissions to regulatory authorities in order to obtain marketing authorization They can be of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.[23-24] In 2013, Doshi and colleagues called for reporting invisible and abandoned trials (RIAT), i.e. trials that have remained unpublished (invisible) and those that suffer from selective reporting and miscoding (abandoned), using CSRs.[25] This is because biased publications have a huge impact on subsequent reviews and therefore on decision-making, where harms of treatments can remain hidden, while their benefits could be exaggerated.[26-27] These impacts can be very catastrophic both in terms of loss of human life (as seen by the disaster with the approval and subsequent removal of Vioxx that increased the risk of heart attacks and stroke, but the data that demonstrated this remained unpublished)[28-30] and also a waste of government resources (as was seen by the stockpiling of Tamiflu [oseltamivir], which has now been shown to have almost no clinical benefit, using previously unpublished data).[31-32] Therefore there is an increased wish for independent meta-analyses of trial data to be conducted to evaluate the safety concerns of drugs and true benefits.[33]

It is essential that systematic reviews give equal attention if not more to studying harms of interventions as well as the benefits, in order to get an estimate of their overall effectiveness but evidence exists that adverse effects data is still very poorly reported on in published literature.[34-36] A study found that many trials with serious adverse events that were posted on the trial registration website ClinicalTrials.gov were not yet published, or if they were, they reported a discrepant number of events as compared to the website.[37] Another recent review found that the information around adverse events remained unpublished or partial and the unpublished sources gave higher values and ranges when compared to their published counterparts.[38]Attempts have been made to improve the reporting of adverse events in trials with the development of an extension of the CONSORT statement in 2004 to address this issue[39] and more recently an extension of the PRISMA guidance to accommodate better guidance for systematic reviews of harms.[40]

The health-related quality of life (HRQoL) measurements have rarely been published or have been reported on selectively from industry sponsored trials.[23] HRQoL scales measure the subjective health and functional status of patients and their general well-being, as seen from their own perspective.[41] A recent review of 101 trials found that HRQoL outcomes were the least reported on, with only 7% having complete information in journal publications when compared to CSRs.[42]

In summary, the selective publication of clinical data (publication bias) and their outcomes (selective reporting) is a major factor in misrepresenting effectiveness of interventions within the scientific literature and as a consequence the perception of the effects of healthcare interventions are biased, and this is especially worse for outcomes of harms and quality of life and therefore this PhD focuses on these outcomes.

1.2 Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors

It has been shown that an overwhelming number of meta-analyses of antidepressant trials have ties to the industry, and these were less likely to have negative statements about the drug than other meta-analyses (odds ratio = 0.02 95% CI 0.003 to 0.18; $p<0.001$).[43] There is also strong evidence to show that journal articles of antidepressant trials are highly selectively published. A comparative study that considered the published literature for 12 antidepressants involving 12,564 patients with data belonging to the Food and Drug Administration (FDA), found that amongst the 74 FDA-registered studies, 31% were not published and the publication was often of the trials with positive results. According to the published literature, 94% of the trials conducted appeared to be positive (statistically significant benefit of the primary outcome), however this was in complete contrast to the FDA dataset and analysis, which showed that only 51% of the trials were in fact positive.[44]

A re-analysis of the CSR data compared to published literature for the use of selective serotonin reuptake inhibitors (SSRIs) for the treatment of depression in children and adolescents, found gross selective reporting in the journal publications.[45] The revised publication of the SSRI paroxetine trial 329 (treatment of unipolar major depression in children and adolescents) using complete data from the CSR also showed that the published article over-estimated the benefit and under-reported serious harms like suicidal behaviour.[46]

The drug paroxetine belongs to the class of SSRIs which were first introduced as alternatives to tricyclic antidepressants in 1980s but have since been prescribed for increasing number of indications and have become one of the most commonly prescribed drugs today.[47-49] These drugs have been shown to inhibit the reuptake of serotonin into the presynaptic neurone, and therefore increase neurotransmission. However, some within the class inhibit the reuptake of noradrenaline (and/or dopamine to a lesser extent) and so therefore they are not very "selective" nor very specific for serotonin.[48] The different serotonin-norepinephrine reuptake inhibitors (SNRIs) block the reuptake of both serotonin and norepinephrine with differing selectivity and are used for similar indications as SSRIs.[50] The SSRIs and SNRIs that are commonly used (regardless of indication) are summarised in Table 1, based on the data available from the FDA and the European Medicines Agency (EMA).

Table 1: Commonly used SSRIs and SNRIs, data taken from FDA and EMA[51-55]

Generic name	**Main brand names (Denmark)**	**Generic name**	**Main brand names (Denmark)**
	SSRIs		***SNRIs***
citalopram	Cipramil	atomoxetine	Strattera
escitalopram	Cipralex	duloxetine*	Cymbalta, Xeristar, Yentreve
fluoxetine*	Fontex	reboxetine	Edronax
fluvoxamine	Fevarin	venlafaxine*/ venlafaxine hydrochloride*	Efexor/ Efexor XR
paroxetine*	Seroxat		
sertraline*	Zoloft		

*drugs for whose trials we could include in this PhD thesis as we received CSRs from the authorities for them.

The effectiveness of these drugs has been long questioned. A recent systematic review showed that the benefit of SSRIs based on the Hamilton Rating Scale for Depression, was below what is clinically relevant (below three points), even when none of the trials included had been compared to active placebos.[56] This is when it has been previously demonstrated that the clinical benefit was even smaller for antidepressants when trials with active placebos were considered instead of inert

placebos due to unblinding effects that inflate effectiveness estimates.[57] Therefore the small benefits seen between the these drugs and placebo may not be clinically meaningful and moreover they could also be partly due to an artefact of unblinding.

These drugs are not only known to have poor benefit but have also been shown to have serious harms related to them. [49,58-61] The increased risk in suicidal behaviour associated with these drugs had been cited in anecdotal cases previously,[49,59] but the expert comprehensive review undertaken by the UK Medicines and Health Regulatory Authority (MHRA) demonstrated this was an established problem amongst children and adolescents taking these drugs.[62] The subsequent systematic review that was undertaken for the National Institute for Health and Care Excellence (NICE) then compared this previously hidden data (now available publically through the expert review) to the published data and found that in all but one case the harms outweighed the benefits.[45] This work also led to another expert review undertaken by the FDA in the US which also confirmed the increased risk of suicidal behaviour amongst young people who found this was the case until the age of 24 years[63] and this lead to a black box warning for these drugs by the FDA for this population.[64] Both organisations also found an increased risk of hostility or aggressive behaviour[62-63] and that was also noted by subsequent research since then,[65-66] but no comprehensive review like the one done for suicidal behaviour had been undertaken for this outcome.

The Nordic Cochrane Centre was successful in obtaining access to CSRs for SSRIs and SNRIs from the European Medicines Agency (EMA) in 2011 after a long battle for access that started in 2007.[28] The centre had already looked at the CSRs for one SNRI (duloxetine) in comparison with its published articles and found there was gross reporting bias (there were trials that remained unpublished and those that were published had been selectively reported on).[67] This PhD thesis takes that work forward and looks at the complete set of CSRs on SSRIs and SNRIs the centre received for serious harms, study drop-out rates and their effect on quality of life of people.

1.3 Objectives

The objectives for the PhD as stated in the PhD proposal were as follows:

1. To determine the degree of selective reporting within CSRs of suicidality, violence and akathisia by comparing the raw data from patient narratives with adverse events tables and

summaries. In a supplementary analysis, we will also include symptoms of activation syndrome and similar events.

2. To determine whether SSRIs/SNRIs cause suicidality and violence in all age groups and to compare our results with those that have previously been published, in particular the meta-analyses undertaken by drug agencies.
3. To determine the quality of life of patients on SSRIs/SNRIs compared to placebo.
4. To publish one or more particularly interesting trials according to the RIAT principle.

In practice the second point of the first objective *("in a supplementary analysis, we will also include symptoms of activation syndrome and similar events"*) could not simply be undertaken as a supplementary analysis as it was a different research question and a large undertaking on its own. It is currently underway as a separate research study. Please see section '3.2 Perspectives for current and further research' for further details on that project.

Moreover, we were able to look at the main part of the first objective along with the second one (considering suicidality, violence and akathisia with relevant age related effects and comparisons with previous meta-analyses undertaken by drug companies) in the first research article together: Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016; 352:i65.

However, on presenting our results from the first study it was brought up that we had used not an optimal method of meta-analysis (Peto's odds ratio) for our rare event data, which can have erroneous results when the two arms are unbalanced.[68-69] Moreover to appropriately compare our results with that previously undertaken by FDA and MHRA, we should also be comparing results that arise using the same method. These criticisms led to the second research article, to ensure the results of the first study were valid: SharmaT, Gøtzsche PC, Kuss O. The Yusuf-Peto method was not a robust method for meta-anlayses of rare events data from antidepressant trials. Journal of Clinical Epidemiology, 2017 Nov;91:129-136.

The third study arose from the details of the research protocol within the PhD proposal ("*..we will also document discontinuation rates and include reasons for discontinuation*…"). This once again

warranted a full separate research study and could not be undertaken on the side as it was a research question on its own merit and due to the volume of the dataset had to be handled separately: Sharma T, Guski LS, Freund N, Meng DD, Gøtzsche PC. Drop-outs rates in placebo-controlled trials of antidepressant drugs: systematic review and meta-analysis based on clinical study reports (Submitted).

The third objective gave rise to the fourth study within this PhD that looked at the reporting bias within the two HRQoL outcomes of EQ-5D and SF-36: Sharma T, Rasmussen K, Paludan-Müller A, Gøtzsche PC. Selective reporting of SF-36 and EQ-5D health related quality of life outcomes in clinical study reports and publications of antidepressant trials, (draft manuscript).

The fourth objective of the PhD proposal was to publish one of the interesting unpublished trials as a RIAT publication.[25] This was not feasible to do in the time available or the resources we had. As shown by the publication of the RIAT version of trial 329 of paroxetine,[46] this should be done with access to case report forms (CRFs) for accuracy. We did not receive any CRFs with the CSRs from the regulators. Therefore we would need to request them from the pharmaceutical companies, which can take up to 6 months to a year. That RIAT publication of study 329 was also the first of its kind and it required the work of seven researchers, four of them working on this full time and it still took those researchers two and a half years to complete. For the lead author this was her complete work for her PhD thesis. Based on discussions with one of the co-authors of that study and our own experience with the research we have undertaken so far, the time and personnel required to do this was not completely appreciated when writing the PhD proposal (work of this nature had never been done previously). Therefore this objective has not been undertaken as part of this PhD but can be something for the centre to continue with in the future.

2 Description of the research project

2.1 Research article 1: *Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. British Medical Journal 2016; 352:i65.*

The first research article is a combination of the project undertaken in order to study the first two objectives of the PhD so "*to determine the degree of selective reporting within CSRs of suicidality, violence and akathisia by comparing the raw data from patient narratives with adverse events tables and summaries..*" and to also "*to determine whether SSRIs/SNRIs cause suicidality and violence in all age groups and to compare our results with those that have previously been published..*".

As noted previously within the introduction (section 1.2) there had been serious concerns with respect to suicidality amongst young people on SSRIs/ SNRIs [45,48, 62-63] but the evidence for adults demonstrated this was not the case.[70] Though reports of increased risk of violent behaviour in young people on these drugs had also emerged[71-79] including that from Medicines and Healthcare products Regulatory Agency (MHRA)[62] and FDA data,[63,65] there was no quantitative comprehensive analysis undertaken for this, like for suicidal behaviour. Akathisia which is defined as "*Medication-Induced Movement Disorder Not Otherwise Specified*" by the Diagnostic and Statistical Manual of Mental Disorders,[80] is a condition induced as a side effect of medications (including SSRIs/SNRIs) that can result in extreme inner restlessness such that a person is at an increased risk for violence or suicide.[49,60,73,79,81-83] Despite these reports, once again no comprehensive review had been undertaken for this outcome.

We undertook a systematic review using CSRs of trials of SSRIs and SNRIs as source documents instead of published journal articles, that we had received from the European and UK regulators (EMA and MHRA) for the serious adverse outcomes of all-cause mortality, suicidality (all suicidal behaviour which included suicides, suicide attempts or preparatory behaviour, intentional self-harm and suicidal ideation), aggressive behaviour and akathisia.

We included all placebo-controlled double-blind RCTs regardless of indication that were not undertaken in healthy volunteers and had data on the safety measures. A pilot was first conducted using 5 CSRs (one for each of the drugs) where the entire CSR was read to help understand the different formats of content within the report and finalise the draft extraction form. The CSRs were converted into a readable PDF format (using OCR function) and relevant pages from the CSRs were extracted as separate documents for use in data extraction. Data was extracted on study information by one researcher and on the study population and outcomes independently by two researchers. The CSRs were searched electronically using terms used by FDA[63,84-85] augmented by additional terms identified by our pilot. However, the electronic searches were not always reliable and additional manual searching of terms was required. For the outcome of akathisia only the specific term "akathisia" was used. We also extracted data on instances of selective reporting within the CSR and for the trials from Eli Lilly, we also compared the CSRs to the online summary documents available publically to determine the level of selective reporting and publication bias between those documents.

We conducted meta-analyses of these rare events, using Peto's odds ratio (OR) with a fixed effect model using RevMan 5.3[86]and included all post randomisation events (if data was available from the lead-out and post therapy phases it was combined with randomised phase data). In trials with multiple intervention arms that were SSRI or SNRI, we combined the data to get a single drug arm.

2.2 Research article 2: *SharmaT, Gøtzsche PC, Kuss O. The Yusuf-Peto method was not a robust method for meta-anlayses of rare events data from antidepressant trials. Journal of Clinical Epidemiology, 2017 Nov;91:129-136.*

We presented the results of the meta-analyses from the first study/ research article at a conference at the end of 2015 and several statisticians mentioned that as we combined different SSRI arms together, our drug and placebo arms were not balanced and therefore our choice of method (Peto's odds ratio), would no longer be applicable and would lead to erroneous results.[68-69,87-88] Additionally, for appropriate comparison with the previously conducted meta-analyses undertaken by FDA[63-70] and MHRA,[89] ideally the same method of rare event meta-analysis should be considered as research has consistently shown that the method chosen can have a great impact on the estimates.[68,87] We therefore decided to undertake this second methods article to compare the

estimates of the meta-analyses of our four serious rare adverse events of all-cause mortality, suicidality, aggressive behaviour and akathisia across the following different methods:

- **Yusuf -Peto method** (used originally for our first research paper) is an old method first described in 1985 and has been commonly used for meta-analyses for rare event data since then.[87-88,90] This method gives the relative weights to the individual trials based on the variance of the effect measure, which in turn is determined by the underlying risk, calculated from the data. Therefore this means that this method is unable to handle studies with null events in both arms (double-zero studies) and these trials are excluded from the meta-analyses.[87-88] This can be problematic as these double-zero studies actually point to no differences between the two treatment arms and therefore, simply removing them can shift the calculated overall meta-analysis effect measure away from the null effect, biasing the results.[91] Additionally, it is felt that simply removing a number of people who participated in relevant trials may not be ethically appropriate.[92]

- **Generalised linear mixed models (GLMM),** is another widely used method that can be used for meta-analyses of binary outcomes. Here we assume the treatment to be a fixed effect with a normally distributed random intercept term for each individual trial such that it permits the correlation of outcomes from people within the same trial but allows the baseline event probabilities between the different trials to be different as long as a normal distribution is followed across the studies.[68,88] This method allows for the inclusion of double-zero studies. There are several estimation methods available and for our study we used the penalised quasi-likelihood (PQL).[88]

- **Conditional logistic regression** was one of the methods used by the FDA for their meta-analyses.[70] Here the binary outcomes are pooled from the different trials such that the events in the different arms are modelled using a binomial distribution.[68] The model's likelihood function conditions out the study effect, accounting for the correlation of patients within the trials such that there is no need for the assumption of distribution for the random intercept effect as needed in the previous GLMM. The conditional likelihood function is then calculated (similar to a Cox proportional hazard) and with the 'the robust sandwich addition' developed by Lin and Wei, the double-zero trials can also be included.[88]

- **Bayesian approach using Markov Chain Monte Carlo (MCMC)** this was the method used by the UK regulator MHRA.[89] It is also a GLMM model but we used the MCMC method with the Bayesian approach, using non-informative prior distributions (N (0, 10,000) for the intercept and the treatment effect and inverse gamma (0.01, 0.01) for the random effects variance (similar to MHRA) were employed.[88-89]

- **Beta-binomial regression model** is also a logistic regression that uses correlated responses and assumes binomial distributions for the events in the treatment arm, but a beta distribution for the control arms with them linked to each other via a regression equation with the standard logit link function.

All five analyses were done for the four outcomes using SAS®, Version 9.4 (SAS Inc., Cary, NC, USA).

2.3 Research article 3: *Sharma T, Guski LS, Freund N, Meng DD, Gøtzsche PC. Drop-outs rates in placebo-controlled trials of antidepressant drugs: systematic review and meta-analysis based on clinical study reports (Submitted).*

The use of objective outcomes such as study drop-out rates have been considered useful in determining the effectiveness of antidepressants.[93] The overall (all-cause) drop-out rates have been used to determine drug acceptability of antidepressants[94-96] and performance indicators for psychotherapy.[97] To get an indication of the tolerability of a drug the drop-outs due to adverse events have been used previously for antidepressants[93-94] and the drop-outs due to lack of effect have also been studied in antidepressants.[98]

As per the first study, for this project we undertook a systematic review of the CSRs we received from the regulators (EMA and MHRA), and included the double-blind placebo controlled RCTs that reported results for drop-outs appropriately (or study discontinuations as written within the CSRs) and were not healthy volunteer studies or cross-over trials. The CSRs were handled as mentioned before and the primary outcome of overall drop-out rate was independently extracted by

two researchers and the secondary outcomes of drop-out rate due to adverse events and due to lack of effect were extracted by one researcher and checked by another. We undertook meta-analyses using the Mantel-Haenszel method (fixed effect model; RevMan 5.3) and for the secondary outcomes where null events were seen also using the beta-binomial method using using SAS®, Version 9.4 (SAS Inc., Cary, NC, USA).

2.4 Research article 4: *Sharma T, Rasmussen K, Paludan-Müller A, Gøtzsche PC. Selective reporting of SF-36 and EQ-5D health related quality of life outcomes in clinical study reports and publications of antidepressant trials (draft manuscript).*

Health related quality of life (HRQoL) instruments capture the overall sense of well-being and satisfaction of people with their current state of health.[99] HRQoL instruments can be both condition specific (tools that can be used only for a particular patient population of a particular disease) or be generic (tools that capture a very broad range of aspects of health status and the consequences of illness in a general manner).[100-101] Generic instruments therefore allow for the comparisons to be made across different disease groups and therefore are used by many policy-makers for decisions around allocating resources. The most commonly used generic validated HRQoL are SF-36 and EQ-5D where the later can be used to calculate quality-adjusted life years (QALYs), one of the main methods used for priority setting.[102-103]

Antidepressant trials have often used HRQoL outcomes within their trials but very little results have been made available through published articles.[49] A large review that included 101 trials that included some antidepressant trials, that compared CSRs to journal publications and other online sources available to the public, found that the HRQoL outcomes were reported on very seldom and only about 7% of the publications had complete data of their results.[42] Additionally, a review of antidepressant trials that looked at quality of life outcomes concluded that the reporting of its results was "*virtually non-existent*". It also questioned the rationale for choosing one instrument versus another in the different trials, as this information was never available.[104] For this study we conducted a structured audit of the data availability for the antidepressant trials that had the HRQoL outcomes of SF-36 and EQ-5D within their protocols, between CSRs, journal publications and data available online.

3 Summary of the results

3.1 Research article 1: Serious harms of SSRIs and SNRIs

Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016; 352:i65.

This study included 70 trials summarised in 68 CSRs (64,381 pages) of trials of five antidepressants: duloxetine, fluoxetine, paroxetine, sertraline and venlafaxine (or venlafaxine extended release) on 18,526 patients. These trials also contained other active comparators (amitriptyline, clomipramine, desipramine, imipramine and trazodone) given to 767 patients.

The CSRs were of differing quality which impacted our ability to detect instances of occurrences of our outcomes of interest. Often details of these serious harms were drafted in individual patient listings in appendices or within patient narratives and were missing or re-worded to milder terms in the main report. As we only received complete appendices for 32 out of the 70 trials, it is likely that true estimates are higher. The trials themselves had serious flaws in their design where limited wash-out periods were noted, 50 trials allowed for sleeping aids, 8 trials allowed the use of benzodiazepines or similar psychoactive drugs and there were concerns about the validity of the data or fraudulent behaviour in three trials (with three centres in one trial of venlafaxine being "*impounded by the Swiss police for fraud"*). This detailed information was simply not available if we only considered published journal articles.

- <u>All-cause mortality:</u> A total of 16 deaths occurred, two prior to randomisation (one in placebo lead-in phase and one in a 12 week open label phase on duloxetine); nine deaths on an SSRI or SNRI, four on placebo (OR= 1.28; 95% CI [0.40 to 4.06]) and one on imipramine post-randomisation. Four of these deaths (all on SSRIs/SNRIs) were misreported in the main report and only identified correctly from the patient narratives. When we compared this to the online summary documents for the subset of the duloxetine and fluoxetine trials, all the eight deaths (six on duloxetine and two on placebo) post-randomisation were noted, but the suicide on duloxetine in the open label phase was missing.

- Suicidality: A total of 155 suicidality events occurred, 13 of which took place prior to randomisation. No significant difference was seen post-randomisation overall in all patients or for adults alone but in children and adolescents the odds were more than doubled on SSRIs/SNRIs, OR = 2.24; 95% CI (1.24 to 4.04). On comparison with the online reports for duloxetine and fluoxetine only two of the 20 suicide attempts were documented in the summaries, while none of the 14 suicidal ideation events were mentioned.
- Aggressive behavior: A total of 65 events of aggressive behaviour occurred with three of them taking place prior to randomisation. Aggressive behaviour occurred more often on SSRIs/SNRIs than on placebo post-randomisation, OR = 1.93; 95% CI (1.26 to 2.95), but it was not significant for adults but in children and adolescents it again more than doubled the odds on SSRIs/SNRIs, OR = 2.79; 95% CI (1.62 to 4.81). Only 10 of the total 25 aggressive behaviour events were noted in the online summary documents of the duloxetine and fluoxetine trials.
- Akathisia: A total of 30 akathisia events occurred (all post-randomisation) and it occurred more often on SSRIs/SNRIs than on placebo, OR = 2.04; 95% CI (0.93 to 4.48), but this difference was not statistically significant and similar results were seen for both sub-group populations by age (adults OR = 2.00; 0.79 to 5.04 and for children and adolescents OR = 2.15; 0.48 to 9.65). Only three of the total 17 akathisia events were noted in the online summary documents of the duloxetine and fluoxetine trials.

3.2 Research article 2: Rare events meta-analysis methods

SharmaT, Gøtzsche PC, Kuss O. The Yusuf-Peto method was not a robust method for meta-anlayses of rare events data from antidepressant trials. J of Clin Epidemiol, 2017 Nov;91:129-136.

The four outcomes of all-cause mortality, suicidality, aggressive behaviour and akathisia were calculated using the five different methods for rare events meta-analysis of: Yusuf-Peto, generalised linear mixed models (GLMM), conditional logistic regression, Bayesian approach using Markov Chain Monte Carlo (MCMC) and finally the beta-binomial method. The effect estimates did show some variation, though they weren't greatly different. However, what we noticed was that the Peto method consistently underestimated the effect and overestimated it's precision (which was exaggerated when the values deviated from 1).

- All-cause mortality: The original value using the Yusuf-Peto method was OR=1.28, 95% confidence intervals (CI) 0.40 to 4.06, and this changed to 1.37 (95% CI 0.42 to 4.49) using the GLMM-PQL method, to 1.29 (95% CI 0.39 to 4.29) using conditional logistic regression, to 1.51 (95% CI 0.47 to 5.52) using the Bayesian approach (GLMM-MCMC) and finally to 1.33 (95% CI 0.39 to 4.49) using the beta-binomial method.
- Suicidality: The original value using the Yusuf-Peto method for adults was 0.81 (95% CI 0.51 to 1.28) and the subsequent estimates for the methods of GLMM-PQL, conditional logistic regression, GLMM-MCMC and beta-binomial were 0.83 (95% CI 0.53 to 1.30), 0.81 (95% CI 0.52 to 1.3), 0.83 (95% CI 0.53 to 1.31) and 0.94 (95% CI 0.52 to 1.70) respectively. For children and adolescents the Yusuf-Peto method was 2.39 (95% CI 1.32 to 4.33) and the subsequent estimates for the methods of GLMM-PQL, conditional logistic regression, GLMM-MCMC and beta-binomial were 2.73 (95% CI 1. 37 to 5.42), 2.64 (95% CI 1.33 to 5.26), 2.87 (95% CI 1.42 to 5.98) and 2.69 (95% CI 1.19 to 6.09) respectively.
- Aggressive Behaviour: The original value using the Yusuf-Peto method for adults was 1.09 (95% CI 0.55 to 2.14) and the subsequent estimates for the methods of GLMM-PQL, conditional logistic regression, GLMM-MCMC and beta-binomial were 0.95 (95% CI 0.49 to 1.86), 1.09 (95% CI 0.55 to 2.15), 0.97 (95% CI 0.50 to 1.91) and 1.15 (95% CI 0.52 to 2.55) respectively. For children and adolescents the Yusuf-Peto method was 2.79 (95% CI 1.62 to 4.81) while the subsequent estimates using the methods of GLMM-PQL, conditional logistic regression, GLMM-MCMC and beta-binomial were 3.01 (95% CI 1. 60 to 5.67), 3.12 (95% CI 1.66 to 5.88), 3.02 (95% CI 1.66 to 5.77) and 2.92 (95% CI 1.26 to 6.78) respectively.
- Akathisia: The original value using the Yusuf-Peto method for adults was 2.00 (95% CI 0.79 to 5.04) and the subsequent estimates for the methods of GLMM-PQL, conditional logistic regression, GLMM-MCMC and beta-binomial were 2.35 (95% CI 0.78 to 7.08), 2.24 (95% CI 0.74 to 6.79), 2.61 (95% CI 0.90 to 9.72) and 3.60 (95% CI 0.78 to 16.67) respectively. For children and adolescents the Yusuf-Peto method was 2.15 (95% CI 0.48 to 9.65) while the subsequent estimates using the methods of GLMM-PQL, conditional logistic regression, GLMM-MCMC and beta-binomial were 2.28 (95% CI 0.44 to 11.8), 2.27 (95% CI 0.43 to 11.9), 2.72 (95% CI 0.53 to 19.6) and 1.60 (95% CI 0.27 to 9.56) respectively.

3.3 Research article 3: Comparative study drop-out rates

Sharma T, Guski LS, Freund N, Meng DD, Gøtzsche PC. Drop-outs rates in placebo-controlled trials of antidepressant drugs: systematic review and meta-analysis based on clinical study reports (Submitted).

The systematic review was able to include 73 trials for five drugs (duloxetine, fluoxetine, paroxetine, sertraline and venlafaxine or venlafaxine extended release) through 71 CSRs that amounted to 67,319 pages. This corresponded to 18,426 people with 11,057 on either an SSRI or SNRI and 7,369 on placebo. Additionally, there were 852 people on other active comparators (amitriptyline, clomipramine, desipramine, imipramine and trazodone). Apart from the shortcomings of the trials noted previously in the first research study, there were also minor discrepancies with the number of patients where a modified intention to treat principle was employed such that the people lost to follow up early in the trial (study participants with missing data on benefits or harms) were not accounted for.

- Acceptability: overall study drop-outs: Overall there were 5,560 study drop-outs post-randomisation within the placebo or SSRIs or SNRIs arms, with more patients dropping out on the drug arm risk ratio (RR) = 1.08 (1.03 to 1.13). When we look at the sub-groups by age this was RR = 1.08 (1.03 to 1.13) for adults and 1.07 (0.95 to 1.21) for children/ adolescents. Additionally, there were 426 study drop-outs on other active comparator drugs in eight trials. A possibly more reliable estimate was the one available from the sensitivity analysis done by removing the trials that had an "enriched" design where a single arm phase on the drug preceded the double-blind phase, where the odds were RR = 1.12 (1.07 to 1.18).
- Tolerability: study drop-outs due to adverse events: A total of 1,634 study drop-outs occurred due to adverse events among the 18,426 patients post-randomisation within the placebo or SSRIs or SNRIs arms, with more patients dropping out on the drug arm, RR = 2.63 (2.33 to 2.96). When we look at the sub-groups by age this was RR = 2.66 (2.34 to 3.02) for adults and RR = 2.38 (1.67 to 3.39) for children/ adolescents. Additionally, there were 155 study drop-outs due to adverse events on other active comparator drugs in eight trials.

- Study drop-outs due to lack of effect: A total of 1,336 study drop-outs occurred due to lack of effect among the 17,767 patients post-randomisation (not all trials reported this outcome and were therefore not included) within the placebo or SSRIs or SNRIs arms. There were more patients dropping out on the placebo arm, RR = 0.47 (0.43 to 0.53), and looking at the sub-groups by age this was RR = 0.46 (0.41 to 0.52) for adults and RR = 2.38 (1.67 to 3.39) for children/ adolescents. Additionally, there were 26 study drop-outs due to lack of effect on other active comparator drugs in eight trials.

3.4 Research article 4: Selective reporting of quality of life outcomes

Sharma T, Rasmussen K, Paludan-Müller A, Gøtzsche PC. Selective reporting of SF-36 and EQ-5D health related quality of life outcomes in clinical study reports and publications of antidepressant trials.

We included all CSRs of double-blind placebo controlled trials of the SSRI or SNRI that included SF-36 or EQ-5D outcomes in their protocol. For five trials it was unclear which instrument was used and no results were available. For four of these trials the CSRs stated that results of the quality of life outcomes were not meant for determining effectiveness and so were not included but would form a special report after all trials were complete. We were able to include 15 trials (19,015 pages of CSRs and data on 4717 patients) with six using SF-36, seven using EQ-5D and two using both HRQoL instruments.

- CSRs: These were highly selective in their reporting of these outcomes, and only three out of eight trials with SF-36 as an outcome had complete results for it and only four out of nine trials with EQ-5D as an outcome had complete results for it. Four of the duloxetine, two of the paroxetine and the one sertraline trial all had either no results data or only incomplete partial results.
- Data available online: From the Eli Lilly website for the duloxetine trials, none of the eight trials had complete information. For the one paediatric trial of paroxetine the full CSR was available online but for the remaining five adult trials we were unable to find any relevant information from the GSK website. No synopsis was available for the one sertraline trial as Pfizer has only trial synopses available for studies from 2007 onwards.

- Publications: The systematic searches identified 15 journal publications corresponding to 11 of the 15 included trials. However, due to poorly reported methodology it was not confirmed whether we had all the correct relevant publications. We requested the three companies for these publications and for the missing results data from within the CSRs. We received publications from Eli Lilly fairly soon, a code to identify the relevant publications from GSK from their website after some correspondence and nothing from Pfizer. We did not get access to the missing results data from any of the companies. From the publications we could get complete results for only two of the 15 trials, with two trials having partial data and no data was available for the remaining 11 trials (for two of these 11 trials, there was no publication).

3 Discussion

Our research clearly demonstrated that by using more complete information available from CSRs, we could get findings that were previously unavailable from journal articles alone. What our research also identified was that CSRs themselves could be of varying quality and as gross selective reporting also occurred within the CSRs, only trials where we had full appendices with individual patient listings of adverse events could be relied upon for correct estimates of harms. However, the RIAT study undertaken by Le Noury and colleagues shed light to the fact that even having access to these appendices may not be sufficient and that CRFs could contain information on harms that never make it to the patient narratives or listings of adverse events.[46] Our comparison with this RIAT publication of study 329 that had access to the CRFs, demonstrated that we did not capture all the suicidality events in our study as we missed CRFs, therefore our values were underestimates.[105] Our research on HRQoL demonstrated that this data was exceptionally poorly reported on even within the CSRs and no real meta-analyses made clinical sense, as drawing any conclusions from such limited, selectively reported results would be biased and unreliable. All data available online was also very limited and selectively reported on. Eli Lilly and Company had the most data available online and they were also the most forthcoming when we contacted all relevant companies for information for our fourth research study. Their online summary reports, though had more information than journal publications, were also not reliable for complete results on harms, nor HRQoL outcomes. Additionally, like the other companies, they did not provide us with any of the missing data we requested.

As reported previously, our research also found that these trials had severe methodological flaws. Three trials had an "enriched" design (only the patients that improved their outcomes and tolerated the drug well in a single arm drug phase were then subsequently randomised). Many trials had limited lead-in periods and as drug withdrawals can be long lasting,[106] this has a significant impact on subsequent comparative measurements of harms. In two trials the CSRs noted that the specified placebo lead-in period within the protocol were not adhered to, as this wasn't always documented it is unclear how often this occurred in practice. Additionally, all post therapy events were not available within the CSRs and as therapy effects can occur for longer than 24 hours (often what was available), our numbers are again likely underestimates.[107] The trials used different coding

dictionaries for recording adverse events, with very few using the most comprehensive Medical Dictionary for Regulatory Activities (MedDRA) dictionary.[24] For example the World Health Organization Adverse Drug Reaction Terminology (WHO-ART) dictionary and the Adverse Drug Experience Coding System (ADECS) developed by GSK did not include the term "akathisia" and this appeared to be coded as 'hyperkinesia' or milder terms of activation, anxiety respectively in trials using these dictionaries. ADECS additionally also used the term "*emotional lability"* to code *" events such as suicidal ideation/gestures as well as overdoses*" despite the dictionary Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART), on which ADECS is based upon containing both suicidal ideation and akathisia terms.[108-109] Furthermore the use of benzodiazepines or similar psychoactive drugs were permitted in some trials and most trials permitted the use of sleeping aids which would obscure the true effects of the SSRIs and SNRIs.

Our research found a significant doubling of both suicidality and aggressive behaviour for children and adolescents on SSRIs and SNRIs compared to placebo. These odds were also found to be even greater when more appropriate methods for meta-analysis of rare events were considered. The MHRA also found that the odds ratios for the different drugs ranged from 1.2 to about 4.5 times than that for placebo, depending on the drug[62] and another previous comprehensive review also concluded that this increased risk was two-fold in young people,[110] which is in line with our work. The FDA's analysis also added serious warnings (black box warning) for increased suicidal behaviour for these drugs for this age group (until 24 years of age)[63-64]. However with the absence of CRFs and problems with coding, we know that our values are still underestimates.

Neither of the regulatory authorities did a comprehensive systematic review or meta-analysis for aggressive behaviour, but both MHRA and FDA did note that there was an increase in hostility in this age group.[62-63] Therefore our work on this outcome was a new finding within the literature. Our review also indicated a possible increased trend for akathisia, but this result was not statistically significant. We did however, have very limited data for this outcome as it was underreported within the CSRs and was often miscoded to other milder activation terms such as nervousness, anxiety etc., but as we did not have access to verbatim terms and individual patient data for all the trials, it was very difficult to get an accurate significant estimate. We also decided to take the conservative approach and only consider the term "akathisia" rather than other terms that have been identified to

describe this phenomenon[81] due to problems with coding (as it wouldn't be possible to determine which activation events were indeed akathisia). We therefore can again say that our values for akathisia are therefore underestimates.

Our research on study drop-out rates demonstrated for the first time that more patients on SSRIs or SNRIs left the study compared to placebo. As this outcome can be considered to represent the patients' overall assessment of benefits and harms, the problems associated with these drugs becomes apparent. The data we received for the HRQoL was very limited and therefore no reliable conclusions can be drawn except that companies have withheld most of the results relating to this outcome, even in CSRs, raising the question of why that would be the case.

Since I started this PhD the data accessibility environment has been rapidly evolving for the better and initiatives have been developed to reduce dissemination bias. CSRs have become available from EMA with their policy to make all newly submitted reports publicly available.[111] This however does not apply to the CSRs received by the agency previously for drugs that have already received marketing authorisation. Moreover problems still persist as CRFs are still only available through a remote desktop, non-downloadable interface that is very user-unfriendly.[46,112] The FDA have also followed suite and have developed a new policy of transparency and have started making data available to the public on medical device reports, enforcement reports, and drug adverse event reports.[112] Some companies have also jointly developed an online platform where independent researchers can request for individual patient level data for their research.[114] The requests submitted by researchers are examined by an independent review panel who then determine whether data should be made available for the research or not. Therefore there are still several hurdles for accessing complete trial data for all trials.

The initiative "All Trials" raises awareness to the problems of dissemination bias and are pushing for further improvements in accessibility of raw trial data for research.[115] As our research identified that the trials themselves were of poor methodological quality and improved access alone would not solve that problem, another initiative "More Trials" is very important in raising the quality of the clinical trials undertaken by industry and is pushing for the minimum requirements to be improved.[116]

3.1 Strengths and limitations of the study

One of the main strengths this research was that it confirmed that we can no longer rely on systematic reviews undertaken using journal articles alone as they are biased and give flawed results. Another major strength of this research was that by using CSRs and previously unpublished data we were able to conduct very comprehensive reviews of the RCT data. We were able to confirm the results for suicidality and our work on aggressive behaviour, akathisia, study drop-out rates and HRQoL gave rise to novel findings. Our review also highlighted major flaws in the trials, in their design and in their reporting, even in the CSRs.

One of the main limitations of this PhD project was that we were limited by the data we received from the regulators. We did not have access to the CSRs for all SSRIs and SNRIs and only had individual patient listings for 32 trials, and CRFs for none of the trials. Moreover the CSRs we did have access to, were of varying quality and detail. Due to the problems of the different coding dictionaries we were unable to determine accurate estimates for akathisia as we took a conservative approach for this outcome. Additionally, we were unable to have the second researcher blinded for data extraction as initially planned within the proposed PhD proposal as a pilot undertaken at the start of the research project illustrated that the format and language of the CSRs meant that redacting the names of the arms of the study were insufficient for blinding.

3.2 Conclusions

Despite the above mentioned limitations my overall conclusions from the cohesive body of research of the four research articles, is that due to problems of dissemination bias, only raw data from clinical trials should be used for conducting systematic reviews in the future. All trials should be registered, their protocols compared to results (at the individual patients level from CRFs) to determine whether selecting reporting of outcomes has occurred or not. All regulatory authorities should provide and make available all data from all trials, so independent researchers can check their decisions, to ensure patient safety. For the results of harms' data, the coding dictionary used and for HRQoL outcomes the instrument used, should be considered alongside the results, to determine bias. Based on my PhD work, the harms of SSRIs and SNRIs seem to overshadow any minimal benefit (which maybe clinically insignificant) in young people and therefore the prescribing in this age group could be considered negligent.

3.3 Perspectives for current and further research

SSRIs and SNRIs have been associated with serious harms but other adverse events such as emotional blunting, lack of empathy or disinhibition and activation syndrome should also be reviewed carefully as they can be considered precursors to suicidality and violent behaviour.[74,117-118] A qualitative study found strong evidence to suggest that the emotional side-effects were significant. There was a general feeling of their emotions being '*dulled*', *'numbed', 'flattened'* or completely *'blocked'*, there was a reduction in positive emotions which were '*dampened down'* or *'toned down'* and people noted a sense of detachment or a '*disconnection'* as if they were a '*spectator'* in their own lives such that they stopped caring about things. Some also felt that their personality had changed and they were a '*shell*' of their previous selves.[119] There is no strict diagnostic criteria for activation syndrome (also referred to as jitteriness syndrome), but in 2004 the Food and Drug Administration (FDA) warned clinicians treating patients with newer antidepressants, about the syndrome citing symptoms including '*anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania'* and that it could lead *to 'potential suicide risk'* and noted that the rates of activation when treated with antidepressants was significantly higher in juvenile anxiety (13.8%) or depressive (9.79%) disorders, when compared to placebo (5.22% and 1.10%, respectively; both $p< 0.0001$). The risk of excessive mood elevation which included psychotic symptoms like mania and hypomania, is also greater on antidepressants than on placebo for children and adolescents (for depression the relative risk was 3.61 (95% CI 1.60 to 8.10 and for anxiety, it was 1.49 (95% CI 1.08 to 2.06).[120-121] Moreover, a recent review of such precursor events in healthy volunteer trials of antidepressants demonstrated a greater risk for those on the drugs (OR = 1.81; 1.05 to 3.12).[122]

Therefore further work on getting more accurate risk of such events is important to understand the true impact of these drugs and also to trigger careful monitoring and evaluation of patients that exhibit them. We are now currently undertaking a systematic review and meta-analysis of the CSRs of double-blind placebo randomised controlled trials where we have individual patient data for all adverse events for these precursor events (32 trials). As we identified many previously unpublished trials within the CSRs that the centre has available to them, RIAT publications of these would be another very useful prospect for future research in this field. What our review of CSRs also demonstrated and has been noted by other researchers working with such documents is that more

consideration and research is needed to re-work the risk of bias tool to include inefficiencies of trials that can only be identified using such rich source documents like CSRs.[122]

4 References

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5 Papers

5.1 Research article 1: Serious harms of SSRIs and SNRIs

Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ* 2016; 352:i65.

Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports

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ABSTRACT

OBJECTIVE

To study serious harms associated with selective serotonin and serotonin-norepinephrine reuptake inhibitors.

DESIGN

Systematic review and meta-analysis.

MAIN OUTCOME MEASURES

Mortality and suicidality. Secondary outcomes were aggressive behaviour and akathisia.

DATA SOURCES

Clinical study reports for duloxetine, fluoxetine, paroxetine, sertraline, and venlafaxine obtained from the European and UK drug regulators, and summary trial reports for duloxetine and fluoxetine from Eli Lilly's website.

ELIGIBILITY CRITERIA FOR STUDY SELECTION

Double blind placebo controlled trials that contained any patient narratives or individual patient listings of harms.

DATA EXTRACTION AND ANALYSIS

Two researchers extracted data independently; the outcomes were meta-analysed by Peto's exact method (fixed effect model).

RESULTS

We included 70 trials (64 381 pages of clinical study reports) with 18 526 patients. These trials had limitations in the study design and discrepancies in reporting, which may have led to serious under-reporting of harms. For example, some outcomes appeared only in individual patient listings in appendices, which we had for only 32 trials, and we did not have case report forms for any of the trials. Differences in mortality (all deaths were in adults, odds ratio 1.28, 95% confidence interval 0.40 to 4.06), suicidality (1.21, 0.84 to 1.74), and akathisia (2.04, 0.93 to 4.48) were not significant, whereas patients taking antidepressants displayed more aggressive behaviour (1.93, 1.26 to 2.95). For adults, the odds ratios were 0.81 (0.51 to 1.28) for suicidality, 1.09 (0.55 to 2.14) for aggression, and 2.00 (0.79 to 5.04) for akathisia. The corresponding values for children and adolescents were 2.39 (1.31 to 4.33), 2.79 (1.62 to 4.81), and 2.15 (0.48 to 9.65). In the summary trial reports on Eli Lilly's website, almost all deaths were noted, but all suicidal ideation events were missing, and the information on the remaining outcomes was incomplete.

CONCLUSIONS

Because of the shortcomings identified and having only partial access to appendices with no access to case report forms, the harms could not be estimated accurately. In adults there was no significant increase in all four outcomes, but in children and adolescents the risk of suicidality and aggression doubled. To elucidate the harms reliably, access to anonymised individual patient data is needed.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Important information on harms is often missing in published trial reports

Clinical study reports should therefore be the preferred source for systematic reviews of drugs

Antidepressants can increase the risk of suicide in children and adolescents

WHAT THIS STUDY ADDS

Despite all the limitations we identified in the trials and in the clinical study reports, we found an increase in events of aggression with antidepressants (lost in adults alone), with a doubling of both suicidality and aggression in children and adolescents

Selective reporting of relevant harms across the different sections of the clinical study reports meant that patient narratives, tables with individual patient listings (often found in appendices), and case report forms are needed for complete information

Online summary reports of trials available from Eli Lilly's website are inadequate as source documents for identifying harms data

Introduction

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are some of the most commonly prescribed drugs.[1,2] SSRI induced suicidality was first reported in 1990[3] but only became generally recognised after a BBC Panorama programme focused on it in 2002.[4]

A 2004 UK review showed a noticeable discrepancy between published and unpublished trials and increased suicidal behaviour in children and adolescents (aged <18 years),[5] which resulted in serious warnings against these drugs being used in this age group.[6] It is widely believed that the risk of suicide is not increased in adults, and support for this was provided by a Food and Drug Administration meta-analysis of about 100 000 patients.[7] However, a large systematic review of published trials found an increase in suicide attempts with SSRI treatment,[1] and another review using data submitted to the UK's Medicines and Healthcare products Regulatory Agency (MHRA) could not rule out an increased risk of suicidal behaviour during early treatment with these drugs.[8]

For aggressive behaviour (for example, hostility, assault) in general, reports are conflicting.[9-15] A UK review using MHRA data found an increase in hostility in children and adolescents,[16] and an analysis of adverse events reported to the FDA showed that antidepressants were disproportionately involved in cases of violence, including murder.[17] Many cases of aggressive behaviour have been reported,[2,4] but, unlike with

suicidality, little systematic research has been undertaken. Perpetrators of school shootings and similar events have often been reported to be users of antidepressants[18] and the courts have in many cases found them not guilty as a result of drug induced insanity.[4]

Akathisia is an extreme form of restlessness, which some patients describe as wanting to "jump out of their skin," that may increase the risk of suicide and violence.[2 4 11 19-25] The *Diagnostic and Statistical Manual of Mental Disorders* describes akathisia or similar activation symptoms as "medication-induced movement disorder not otherwise specified."[26]

Clinical study reports are detailed summaries of trial results prepared by the drug industry for submission to regulatory authorities to obtain authorisation for marketing. A recent review of clinical study reports showed that essential information on patient relevant outcomes was often missing in the published articles.[27] Research undertaken by our centre using nine clinical study reports on duloxetine found that data on major harms was missing from journal articles and in summary trial reports.[28] We did not have access to any case report forms (paper or electronic questionnaires that contain the collected data on each participant in the trial), although they would have been the ideal information source.[28]

We report here our results for mortality, suicidality, aggression, and akathisia based on clinical study reports for five different antidepressants.

Methods

In 2011, we requested clinical study reports on SSRIs and SNRIs from the European Medicines Agency and the UK's MHRA. We did not get access to clinical study reports for all trials or for all the commonly prescribed drugs, and we did not receive case report forms for any of the trials. One researcher (TS) selected those clinical study reports that described double blind placebo controlled trials and which contained patient narratives (brief summaries of deaths, serious adverse events, or other events of clinical importance) or listings of adverse events in individual patients (with details such as patient identifier, the adverse event (preferred term and verbatim term), duration, severity, and outcome).[28]

We were able to include five drugs: duloxetine, fluoxetine, paroxetine, sertraline, and venlafaxine (or venlafaxine extended release). We converted the clinical study reports to readable portable document format, and one researcher (TS) copied all relevant pages—with study information, protocols, all adverse event summaries and tables, relevant appendices (where available), patient narratives, and individual patient listings—for use in data extraction.

As a pilot, we randomly chose one report for each drug and read it in its entirety to help understand the different formats of the clinical study reports and to refine the data extraction form. We had planned that the second observer would extract the data blindly, with the treatment groups masked, but the pilot showed that the format and language used made blinding impossible. The primary researcher (TS) and a second observer (LSJ or NF) extracted data from the selected pages of all the clinical study reports independently; disagreements were resolved by discussion and documented using κ statistics (see supplementary data A).

Outcomes

The primary outcomes were mortality and suicidality (suicide, suicide attempt or preparatory behaviour, intentional self harm, and suicidal ideation); secondary outcomes were aggressive behaviour and akathisia. To identify the primary outcomes, we used the same terms and phrases as those of the FDA[7 29] and added additional terms from our pilot. We searched the clinical study reports both electronically and manually. For people with more than one suicidality event, we counted only the most severe one, whereas this was not possible for the secondary outcomes, which only allowed us to count events. Terms for aggressive behaviour were informed by the pilot, and akathisia was identified by searching for "akathisia" in the text (see supplementary data A). All relevant events were classified using the *Medical Dictionary for Regulatory Activities* (MedDRA) coding dictionary. For duloxetine and fluoxetine, we compared the data with the summary trial reports from Eli Lilly's website.[30]

For meta-analysis of rare events, we reported odds ratios using Peto's exact method and calculated 95% confidence intervals with a fixed effect model using RevMan 5.3.[31 32] All post-randomisation events were included, so when data from the lead-out and post-treatment phases were available, we combined them with the data from the randomised phase. In trials with multiple intervention arms, we added the data on arms arithmetically to get a combined drug arm. We planned and conducted subgroup analyses for adults for all outcomes and for suicides and suicide attempts combined, and did post-hoc analyses for suicides and children and adolescents and a sensitivity analysis removing data from fraudulent centres, as suggested by peer reviewers.

Patient involvement

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. We plan to involve patient organisations in the dissemination of our results.

Results

We excluded 125 of the 198 clinical study reports: 96 were not double blind placebo controlled trials, 28 were studies in healthy volunteers, and one was a crossover trial (fig 1). Of the remaining 73 clinical study reports, we excluded five that had no patient narratives or individual patient listings of adverse events. The 68 included clinical study reports amounted to 64 381 pages and corresponded to 70 trials.

Trial characteristics and study design

The experimental drugs were duloxetine (23 trials), fluoxetine (n=3), paroxetine (n=8), sertraline (n=28), and venlafaxine (n=8). In total, 10 258 patients received a

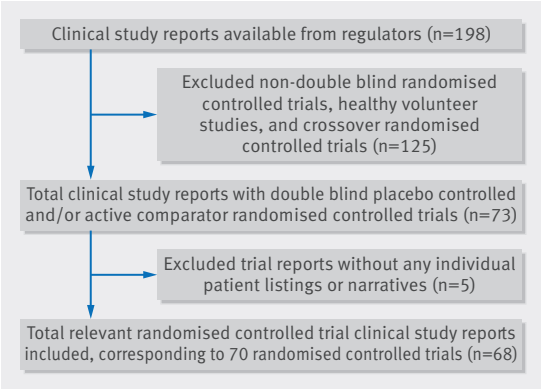

Fig 1 | Flowchart showing selection of relevant studies for inclusion

drug and 6832 a placebo. Fifteen trials had an additional (SSRI or SNRI) comparator in 669 patients (228 receiving fluoxetine and 441 receiving paroxetine) and a tricyclic or tetracyclic comparator in 767 patients. Eleven of the trials (12% of the patients) concerned children and adolescents. Table 1 shows the indications for treatment; 34 trials included 7882 patients with major depressive disorder. Patients at risk of suicide were excluded in 44 trials (63%); in 16 trials, suicide risk was not an exclusion criterion (23%), whereas it was unknown in 10 trials (14%). The randomised phase of the trials lasted from one to 54 weeks (median nine weeks).

Sixty trials (86%) had a placebo lead-in period (4 to 14 days, median 7 days) and all of them excluded from randomisation those who improved while receiving placebo, as judged by their Hamilton scores or similar. Rarely was there any information about the numbers excluded.

It was unclear to what extent sedatives were allowed or used. Four duloxetine trials and four sertraline trials allowed benzodiazepines or similar psychoactive drugs. However, in at least 50 trials (71%, we did not have access to the full protocol for all the trials), sedatives such as choral hydrate or zolpidem were allowed if the patients had difficulty sleeping.

The quality of the clinical study reports varied. For 32 trials we had individual patient listings of adverse events for all patients (in appendices, apart from the venlafaxine trials where the listings were part of the main report). We had access to the protocol for 44 trials; for the remaining trials, only a summary of the study design was available. It seemed that all other appendices were either only "available on request" to the authorities or came under "the system of exceptions set out in the Regulation (EC) No 1049/2001," and so could not be released to us. This is in line with the guidance for clinical study reports, where certain appendices are not required to be submitted to the EMA.[33] For 27 trials, we only had abbreviated or summary clinical study reports; some of these were titled accordingly whereas others were called clinical study reports, although they were only short summaries of about 100 pages. For four trials of sertraline, we only had summary reports combining two trials each (trials 51 and 52, and trials 53 and 54) for which the protocols were the same. We analysed the results accordingly. Key characteristics of the included trials are available in the supplementary data B.

The drug companies had concerns about the validity of the data or fraudulent behaviour in three trials. The data from one centre in trial 28 was not included in the efficacy analyses "due to concerns over the validity of the data," and in trial 34, one centre was shut down "following an internal audit that detected significant compliance violations." Four centres in trial 70 exhibited potentially fraudulent behaviour: three centres had their study records "impounded by the Swiss police for fraud"; and for the fourth centre, "Many of the enrolled patients . . . had identical evaluations for consecutive visits, and . . . all 35 patients from this site had very similar evaluation patterns."

The interobserver agreement for our assessments was high (κ=0.94). Most disagreements resulted from errors in data extraction; discussion and consensus was needed for only two events.

Mortality

Sixteen deaths occurred, all in adults: one in the placebo lead-in phase and one in a 12 week lead-in phase during treatment with duloxetine 60 mg/day. Post-randomisation, nine deaths occurred during treatment with an SSRI or SNRI and four with placebo (odds ratio 1.28, 95% confidence interval 0.40 to 4.06) plus one with imipramine (table 2 , fig 2, and supplementary data C). As none of the deaths occurred in fraudulent centres, no sensitivity analysis was needed.

Four deaths were misreported by the company, in all cases favouring the active drug. One death in a

Table 1 | Overview of indications in 70 trials

Indication	Drugs (No of trials)
Major depressive disorder	Duloxetine (12), fluoxetine (2), paroxetine (3), sertraline (9), venlafaxine or venlafaxine extended release (8)
Obsessive compulsive disorder	Fluoxetine (1), paroxetine (1), sertraline (7)
Post-traumatic stress disorder	Paroxetine (3), sertraline (4)
Stress urinary incontinence	Duloxetine (8)
Panic disorder	Sertraline (5)
Generalised social phobia or social anxiety disorder or social phobia	Sertraline (2), paroxetine (1)
Irritative symptoms of benign prostatic hyperplasia	Duloxetine (1)
Diabetic peripheral neuropathic pain	Duloxetine (1)
Fibromyalgia	Duloxetine (1)
Non-insulin-dependent diabetes mellitus	Sertraline (1)

Table 2 | Number of all cause mortality events in 70 included trials

Phase of trial	No of deaths			
	Before randomisation	Drug arm	Third arm (imipramine)	Placebo arm
Before randomisation	2	0	0	0
Randomised phase	0	8	1	3
Lead-out and post-treatment	0	1	0	1
Total No of deaths	2	9	1	4

Drugs: duloxetine, fluoxetine, paroxetine, sertraline, venlafaxine.

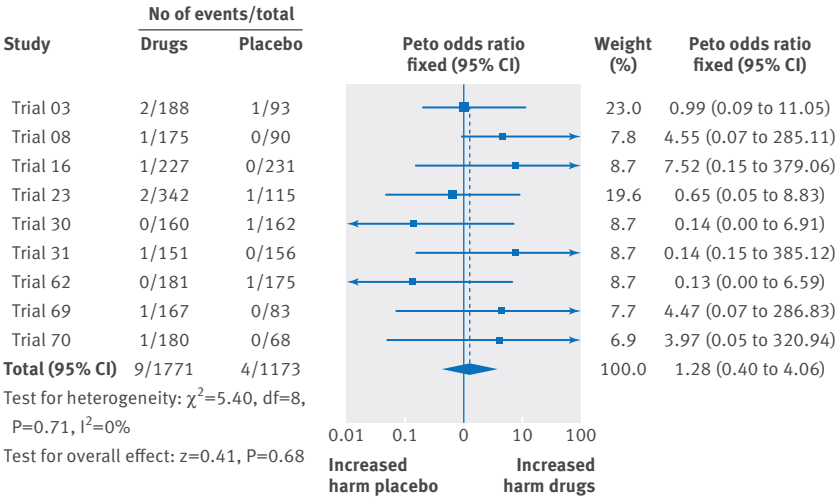

Fig 2 | Meta-analysis of all cause mortality for selective serotonin reuptake inhibitors (SSRI s) or serotonin-norepinephrine reuptake inhibitors (SNRI s) compared with placebo post-randomisation

participant receiving paroxetine (trial 31) was called a post-study event, taking place 21 days after the patient had admitted to taking the last dose, but this was on day 63 out of the 84 days of randomised treatment. Moreover, the patient had detectable paroxetine in the blood at the time of death. A patient receiving venlafaxine (trial 69) attempted suicide by strangulation without forewarning and died five days later in hospital. Although the suicide attempt occurred on day 21 out of the 56 days of randomised treatment, the death was called a post-study event as it occurred in hospital and treatment had been discontinued because of the suicide attempt. Conversely, a patient receiving placebo (trial 62) died on day 404, 26 days after the randomised phase ended, but the death was not listed as a post-study event as the patient had allegedly taken treatment until the previous day. Finally, a death in a participant receiving venlafaxine (trial 70) that occurred three months after treatment was only noted in the patient narratives and nowhere else in the clinical study report.

Suicidality

Overall, 155 suicidality events took place, 13 before randomisation. The odds ratio post-randomisation for suicidality in patients was 1.21 (95% confidence interval 0.84 to 1.74) and was similar for number of suicidality events (1.14, 0.80 to 1.64). The odds ratio for suicidality in adults was 0.81 (0.51 to 1.28) and 0.77 (0.49 to 1.21 for events) and for children and adolescents was 2.39 (1.31 to 4.33) and 2.24 (1.24 to 4.04 for events). None of the suicidality events occurred in patients from fraudulent centres. See table 3 , fig 3 and supplementary data C and D.

Suicides

Six suicides were reported, one in the duloxetine lead-in phase. Post-randomisation five suicides were reported: two in the study drug group, two in the placebo group (odds ratio 0.58, 95% confidence interval 0.07 to 4.48), and one in the imipramine group (see supplementary data C and D).

Suicide attempts

We counted all attempted suicides, including intentional self harm (for example, slitting of wrists), intentional overdoses, and obvious preparatory events (for example, putting a knife to the wrist or neck, but being stopped before any harm). Six of the 73 events (n=70 patients) took place before randomisation (four in participants taking duloxetine and two in participants taking placebo).

One of the events, in a participant taking placebo before randomisation, occurred on day 29, although the lead-in phase was supposed to last only 14 days. Also, one of the four suicide attempts in participants taking duloxetine before randomisation was only identified by

Table 3 | Overall suicidality events in 70 included trials, before and post-randomisation

Suicidality events	Duloxetine	Fluoxetine	Paroxetine	Sertraline	Venlafaxine	All drugs	Placebo	Imipramine
Before randomisation								
Drug event:								
Suicides	1	—*	—*	—*	—*	1	0	—*
Suicide attempts	4	—*	—*	—*	—*	4	2	—*
Suicidal ideation	4	—*	—*	—*	—*	4	2	—*
Suicidality	9					9	4	
Post-randomisation								
Drug (any arm) event:								
Suicides	1	0	0	0	1	2	2	1
Suicide attempts	8	5	18	9	3	43	22	2
Suicidal ideation	8	1	18	11	3	41	25	4
Suicidality	17	6	36	20	7	86 in 85 patients	49 in 46 patients	7 in 7 patients
Total population	4277	456	1766	3165	1263	10927	6832	767

*No patients received these drugs pre-randomisation.

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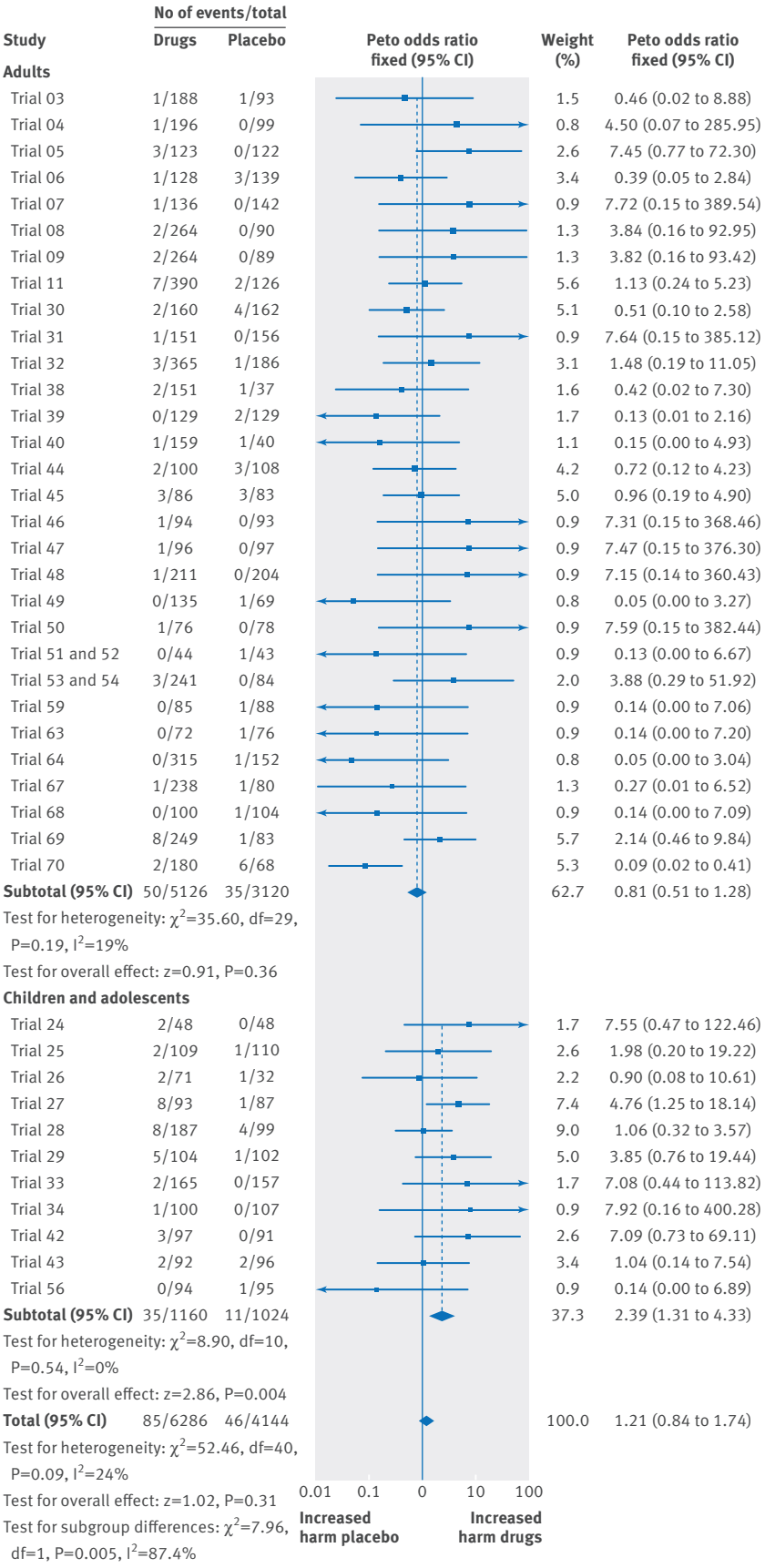

Fig 3 | Meta-analysis of suicidality in participants receiving selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) compared with placebo post-randomisation

going over the appendices containing individual patient listings. This "possible suicide attempt" was listed as "mild" and was not documented elsewhere in the clinical study report and there was no patient narrative.

Five of the 67 post-randomisation events occurred during the lead-out or post-treatment phase of the trials (in three patients receiving study drugs and in two receiving placebo).

Of the remaining 62 suicide attempts (in 59 patients), 40 occurred in 39 patients receiving the study drug, 20 in 18 patients receiving placebo, and two in two patients receiving imipramine. Four of these events were only listed in the individual patient listings and three others only noted in adverse events tables (no further information was available as there was no narrative). Twenty seven events were coded as emotional lability or worsening depression, although in patient narratives or individual patient listings they were clearly suicide attempts. Conversely, several cases of suicidal ideation were called suicide attempts in the adverse events tables. One suicide attempt (intentional overdose with paracetamol (acetaminophen)) in a patient receiving fluoxetine was described as "elevated liver enzymes" in the adverse events tables, in contrast with the narrative (see supplementary data C). There was no difference between suicides and suicide attempts (odds ratio 1.05, 95% confidence interval 0.63 to 1.75). The odds ratio for adults was 0.60 (0.29 to 1.24) and for children and adolescents was 1.85 (0.90 to 3.83, see supplementary data D).

Suicidal ideation

Seventy five participants experienced 76 suicidal ideation events, of which six events were in the lead-in phase (four were taking duloxetine and two placebo). Two of the four events in the duloxetine users were severe and had patient narratives. A third event was mild and was only recorded in treatment emergent adverse events tables. The fourth event, mild suicidal thoughts, appeared only in the appendix containing individual patient listings. Of the 70 post-randomisation events, 41 occurred in participants receiving study drugs, 25 in those receiving placebo, and four in those receiving imipramine.

Sixty two patients experienced 63 events during the randomised phase of the trials (34 events in those receiving drugs, 25 in 24 participants receiving placebo, and four in participants receiving imipramine). Thirty two of these events were coded as emotional lability or worsening of depression in the treatment emergent adverse events tables, but it was clear from the patient narratives or individual patient listings that they were in fact ideation events.

Seven events occurred in the lead-out or post-treatment phases of the trials, and all in participants receiving the study drug (see supplementary data C).

Aggressive behaviour

Three events of aggressive behaviour in participants receiving duloxetine and two in participants receiving placebo took place before randomisation. Post-randomisation there were 62 events in participants receiving the study drugs, 28 in participants receiving placebo, and four in

Table 4 | Aggressive behaviour events in 70 included trials, before and post-randomisation

Events	Duloxetine	Fluoxetine	Paroxetine	Sertraline	Venlafaxine	All drugs	Placebo	Imipramine
Before randomisation	3	0	0	0	0	3	2	0
Post-randomisation (any arm)	7	6	31	14	4	62	26	4
Total population	4277	456	1766	3165	1263	10 927	6832	767

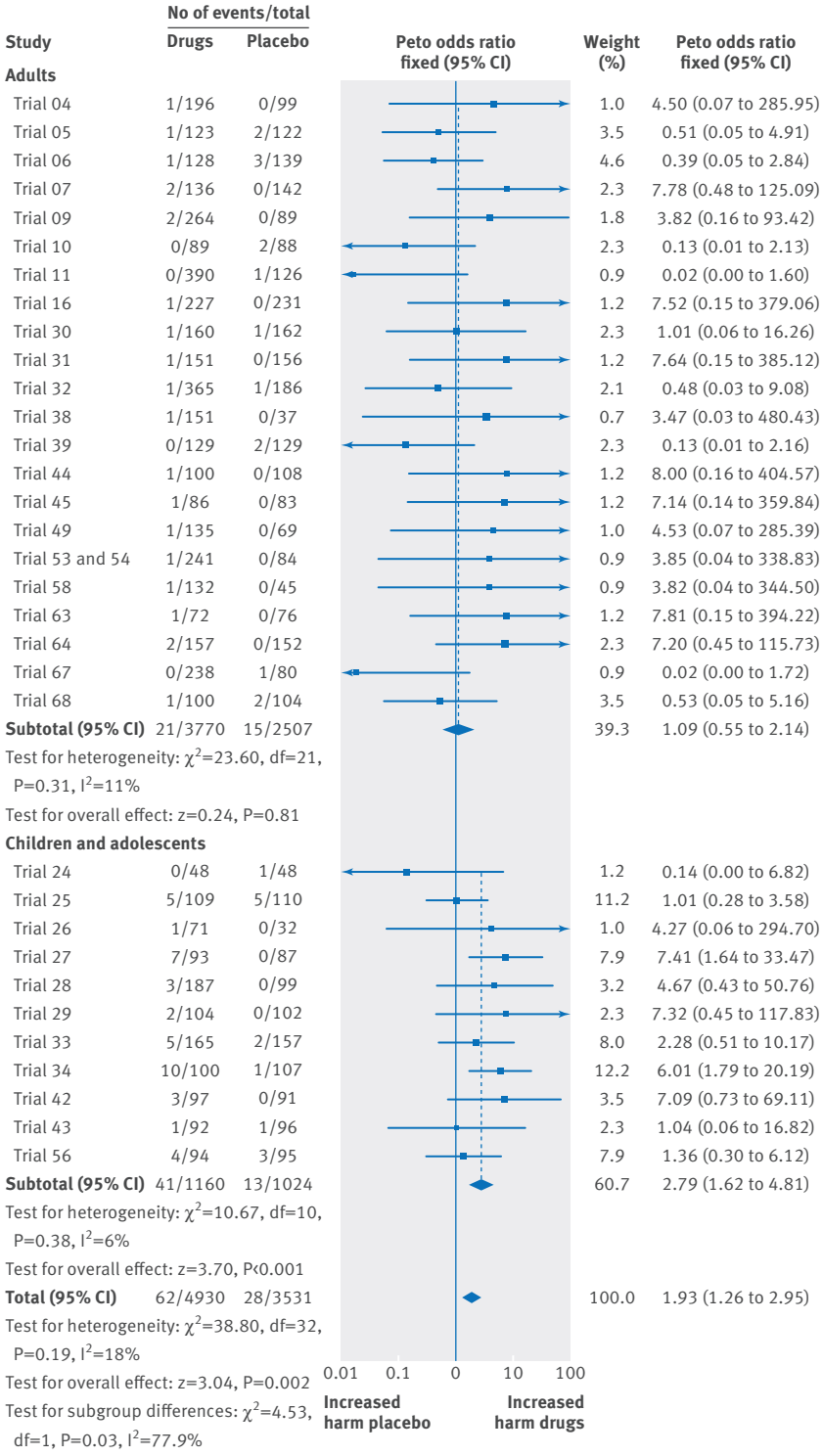

Fig 4 | Meta-analysis of aggressive behaviour in patients receiving selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) compared with placebo post-randomisation

participants receiving imipramine, of which three in the paroxetine group and two in the placebo group occurred in the lead-out or post-treatment phase (table 4). Aggressive behaviour occurred more often in the drug group compared with placebo group (odds ratio 1.93, 95% confidence interval 1.26 to 2.95). The odds ratio for adults was 1.09 (0.55 to 2.14) and for children and adolescents was 2.79 (1.62 to 4.81, figure 4). If data were removed from trials 28 and 34 (paediatric trials in which each centre had fraudulent data), the increase in aggression remained: all ages 1.58 (1.00 to 2.51) and children and adolescents only 2.19 (1.17 to 4.11, see supplementary data D).

Only patient narratives were available for serious events and they included homicidal threat, homicidal ideation, assault, sexual molestation, and a threat to take a gun to school (all five participants receiving sertraline), damage to property, punching household items, aggressive assault, verbally abusive and aggressive threats (all five participants receiving paroxetine), and belligerence (fluoxetine). Details were unavailable for non-serious events, as they were either listed in adverse events tables or given in the appendix of individual patient listings without any narratives. These events were increased hostility, aggressiveness, rage, or anger.

Akathisia

Thirty akathisia events occurred, all post-randomisation (22 in participants receiving study drugs, six in participants receiving placebo, and two in participants receiving clomipramine); two of the events, both in participants receiving duloxetine, took place in the lead-out phase (table 5). Akathisia occurred more often in participants receiving the study drug than in those receiving placebo (2.04, 0.93 to 4.48), but this difference was not statistically significant: for adults 2.00 (0.79 to 5.04) and for children and adolescents (2.15, 0.48 to 9.65, fig 5). If data were removed from trial 70 (adults), where some centres had fraudulent data, the odds ratio becomes 1.99 (0.90 to 4.44) and for adults becomes 1.94 (0.75 to 4.99, see supplementary data D).

Some events were not listed as akathisia in the adverse events tables because of the coding dictionaries used. For example, in the three sertraline trials where we had access to both the verbatim and the coded preferred terms, akathisia seemed to have been coded as "hyperkinesia" according to the World Health Organisation Adverse Drug Reaction Terminology dictionary. We could only identify akathisia if we had access to the verbatim terms, which were sometimes available from individual patient listings or patient narratives. For most duloxetine and fluoxetine trials, akathisia was also noted in the regular adverse events tables, and therefore the trials appeared to have more events than those for other drugs for which akathisia

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Table 5 | Akathisia events in 70 included trials, post-randomisation (no events noted previously)

Drug (any arm)	Duloxetine	Fluoxetine	Sertraline	Venlafaxine	All drugs	Placebo	Clomipramine
Akathisia events	12	7	2	1	22	6	2
Total population	4277	456	3165	1263	10927	6832	767

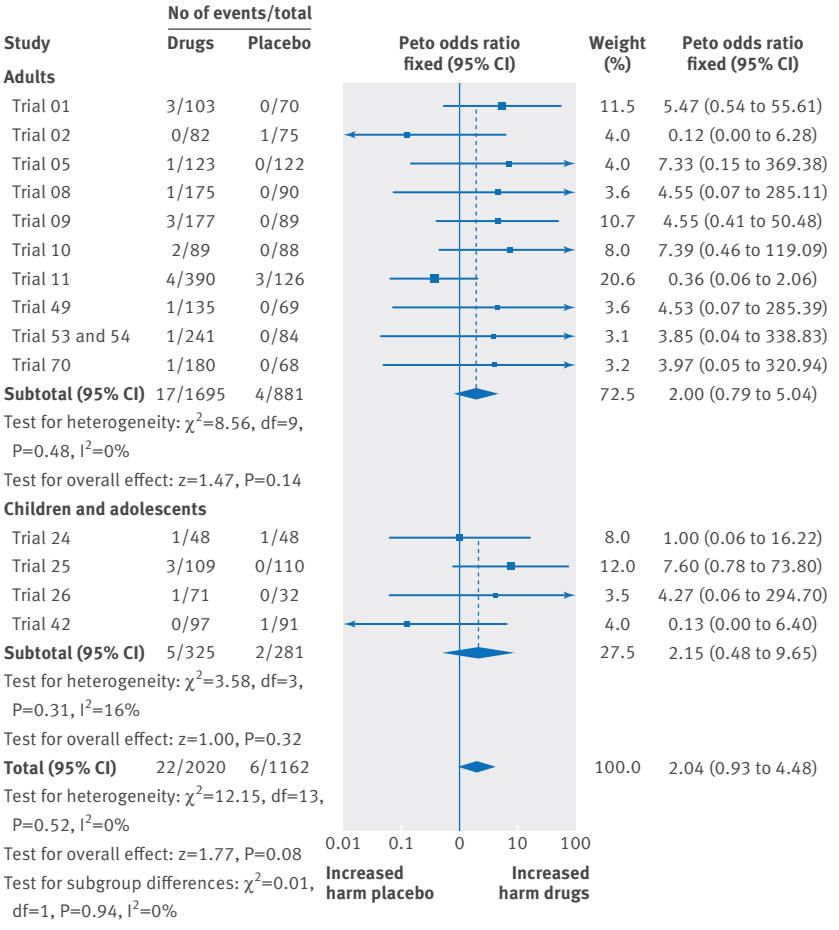

Fig 5 | Meta-analysis of akathisia in participants receiving selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) compared with placebo post-randomisation

was miscoded—for example, no cases of akathisia were reported in the paroxetine trials. These events would be missed in trials where such detailed information was not available. Therefore our number of akathisia events is likely to be an underestimate, as the event appeared to be have been coded under many other activation terms, such as irritability, agitation, or nervousness.

Comparison of our data with the summary trial reports on Eli Lilly's website

Information was limited on adverse events in these summary reports and it was not reliable. The number of serious events was always mentioned but the cases were not always explained and the reports focused on the most common adverse events. All reports contained tables of treatment emergent adverse events, but not for all patients (with the exception of trials 23 and 26 where complete data were tabulated), and in most cases the events were only shown if they occurred in, for example, at least 5% of patients. We were unable to find the online summary reports for four trials (trials 19-22, all on duloxetine). All the eight deaths (six in participants receiving duloxetine and two in participants receiving placebo) post-randomisation were noted in the online summaries, although information on one suicide in a participant receiving duloxetine in the open label phase before randomisation in trial 7 was missing, as no data from that phase were available online. Only two (both participants receiving fluoxetine) of the 20 suicide attempts (14 participants receiving duloxetine, three fluoxetine, and three placebo) were documented in the summaries, and none of the 14 suicidal ideation events (eight in participants receiving duloxetine, two paroxetine, one fluoxetine, and three placebo) were mentioned. Only 10 (three participants receiving fluoxetine and seven placebo) of the 25 aggressive behaviour events (five participants receiving duloxetine, six fluoxetine, and 14 placebo) were found online. Only three akathisia events (all participants receiving fluoxetine) of the 17 (10 receiving duloxetine, five fluoxetine, and two placebo) were in the summaries. However, the case of the "elevated liver enzymes" in a patient receiving fluoxetine in trial 26 was clarified as an intentional overdose.

Discussion

Systematic reviews of harms are needed for a balanced view of medical interventions, particularly to elucidate the occurrence of rare but serious events.[3 4] Clinical study reports are far more reliable than published trial reports,[2 4 28] but even using these we were unable to unravel the true number of serious harms. The trials had many shortcomings, in both the design and the reporting of the trials in the clinical study reports, and therefore our numbers are likely to be underestimates. The summary reports on Eli Lilly's website were even more unreliable than we previously suspected.[28] Only mortality had (almost) complete information.

Comparison with other studies

We found no significant differences in mortality or suicidality overall, but our data confirmed the increased risk of suicide in children and adolescents.[5 16] We wanted to clarify these risks in adults and found no significant increase in association with drugs, similar to previous analyses.[7 8] Our results however, cannot be compared easily with the results of the 2006 FDA meta-analysis[7] as we had data from 18526 patients, whereas the FDA included about 100000 patients. The FDA did not consider the limitations of the trials that we identified and introduced some of their own—for example, by only counting events within 24 hours after the randomised phase was over. We counted all post-randomisation events in our study, although they were not always available. Interestingly, an FDA employee published a

paper in 2001 using FDA data that showed 22 suicides in 22 062 patients randomised to antidepressants,[35] which equates to 10 per 10 000 population, but in the large FDA meta-analysis five years later, five suicides were reported in 52 960 patients, or 1 per 10 000 population.[7]

A review with over 40 000 patients using data submitted to the UK's Medicines and Healthcare products Regulatory Agency (MHRA) also found no increased risk for suicidality in adults using serotonin reuptake inhibitors (SSRIs), but noted that the relative frequency of reported self harm and suicidal thoughts in the trials compared with suicide indicated that non-fatal endpoints were under-recorded.[8] Another review, with 87 650 patients (all ages), reported a doubling in the odds of suicide attempts, which was statistically significant,[1] in contrast with our findings in adults. As with our study, both reviews found serious limitations in the trials and evidence of under-reporting of serious harms.

This under-reporting was also confirmed in the recent republication by independent investigators of study 329 of paroxetine in children and adolescents.[36] We did not get access to the appendices of this trial, which contained the individual patient listings. Many suicidal events were only documented there, and even more suicidal events were only identified in the case report forms, which the investigators got access to after protracted negotiations with GlaxoSmithKline and then only through a single screen remote desktop interface, which made it impossible for the researchers to review all 77 000 pages.[36]

We found that the risk of aggressive behaviour was doubled with use of antidepressants (all ages), which was a statistically significant result, but when we restricted our analysis to adults, there was no such effect. However, we did find a doubling of risk for children and adolescents, which is consistent with the increased incidence in hostility noted by the MHRA.[16] We found that akathisia was much under-reported. Akathisia occurred more often in participants receiving drugs than receiving placebo, both in children and adolescents and in adults, but the difference was not significant (all ages, odds ratio 2.04, 95% confidence interval 0.93 to 4.48). We also found similar results in a systematic review of trials in healthy adult volunteers that included data from 10 published trials and two unpublished trials (clinical study reports obtained from EMA). Compared with placebo (n=226), antidepressants (n=318) were associated with an increased rate of activation or other precursor events for aggression and suicidality (odds ratio 1.81, 95% confidence interval 1.05 to 3.12).[37]

Limitations in the trials and clinical study reports

In most trials (86%), patients were only randomised if they failed to improve in the placebo lead-in period. One large trial had a 12 week open label period where 533 patients received duloxetine and only 278 patients (52%) who tolerated the drug were randomised. This gives rise to response based selection bias, which has an impact on the subsequent randomised phase. During that open label period for duloxetine, there was one suicide (by hanging), four suicide attempts, and four suicidal ideation events.

Another problem was insufficient lead-in periods.[4 24] At least 36 trials had insufficient wash-out periods, lasting for only a few days or a week. An additional nine trials had no lead-in period. Even when a placebo lead-in period was specified it was not always adhered to—for example, in a venlafaxine trial (trial 70), the wash-out period was inadequate in 30 patients who received drugs before the study, and in a sertraline trial (trial 50) it was stated that "some patients proceeded to double-blind treatment without a prior placebo run-in." As patients are often receiving treatment with similar drugs already, some may develop withdrawal effects when they are switched to a placebo,[2 4 12 14 23 24] which can be wrongly counted as adverse events. These iatrogenic harms can be substantial. In a large study supported by Eli Lilly, withdrawal symptoms were registered in patients during a 5-8 day period; 4-24 months after their depression had remitted. Placebo was substituted for active drug, unknown to the patients, and when the patients were switched to placebo, about one third receiving sertraline or paroxetine became agitated, irritable, reported worsened mood, and their Hamilton depression score increased by at least 8.[38]

Most trials did not report on post-treatment events. As previously noted, the FDA included events occurring within the first 24 hours after the randomised phase ended.[7] For sertraline trials in adults (the report's table 30; we reanalysed this summary data), there was no increased risk of suicide or suicide attempts (risk ratio 0.87, 95% confidence interval 0.31 to 2.48).[7] When Pfizer analysed its trial data, the results looked much better for sertraline (we reanalysed their data for suicide or suicide attempts); risk ratio 0.52 (0.17 to 1.59).[39] However, Pfizer published an additional analysis where the patients were followed up for 30 days after the randomised phase ended and then sertraline did not seem to protect against suicides or suicide attempts in adults but rather seemed to cause them (we reanalysed their data, risk ratio 1.47, 0.77 to 2.83), even though these findings were not significant.[39] The investigators who used MHRA data[8] found that when events after 24 hours were included, the risk of suicide or self harm was doubled with sertraline: we reanalysed the data (risk ratio 2.14, 0.96 to 4.75), although the finding was not statistically significant (see supplementary data D).[7]

Another limitation was the use of different coding dictionaries; 32 trials (46%) did not state which one they used. Sixteen of the sertraline trials used the World Health Organisation Adverse Drug Reaction Terminology, and as it does not allow for coding of akathisia or suicidal ideation, such events are most likely to be underestimated in our review. Furthermore, we found that many suicidal ideation events were coded as "worsening depression" or "emotional lability" in treatment emergent adverse events tables in the paroxetine trials, which used their own dictionary (the Adverse Drug Experience Coding System, ADECS), as has been noted by other studies.[36 40] Only one trial (trial 27) mentioned this problem in the clinical study report, which stated that "emotional lability captures events such as suicidal ideation/gestures as well as overdoses." We

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could not find any akathisia events in the paroxetine trials, as we did not have access to the verbatim terms and the events were coded as other activation terms despite akathisia being the preferred term in the Coding Symbols for a Thesaurus of Adverse Reaction Terms dictionary, on which ADECS is based.[41]

Minor tranquillisers and sleeping aids were used in many of the studies, which tend to obscure aggression and akathisia events. Additionally, two thirds of all trials excluded patients at risk of suicide.

Strengths and limitations of this review

We believe ours is the first comprehensive review of randomised controlled trial data using clinical study reports for aggressive behaviour and akathisia, and our finding of the doubling of aggression in children and adolescents is novel. Our review has highlighted limitations in the trials, not only in their design but also in their reporting in the clinical study reports, which may have led to serious under-estimation of the harms.

A main limitation of our review was that the quality of the clinical study reports differed vastly and ranged from summary reports to full reports with appendices, which limited our ability to detect the harms. Our study also showed that the standard risk of bias assessment tool was insufficient when harms from antidepressants were being assessed in clinical study reports. Most of the trials excluded patients with suicidal risk and so our numbers of suicidality might be underestimates compared with what we would expect in clinical practice. We also did not have access to case report forms and because of coding problems we deliberately took a conservative approach and used only one term for identifying akathisia.

Conclusions and implications for research and practice

We believe our study shows that, despite using clinical study reports, the true risk for serious harms is still uncertain. The low incidence of these rare events and the poor design and reporting of the trials makes it difficult to get accurate effect estimates.

The FDA has advised that antidepressants may also cause suicide in young adults (18 to 24 years) and recommends that "patients of all ages" treated with antidepressants should be monitored for "clinical worsening, suicidality, and unusual changes in behaviour."[42] GlaxoSmithKline also issued letters to doctors, informing them about the increased harm in young adults[6] and admitted that for adults with depression "(all ages), the frequency of suicidal behaviour was higher in patients treated with paroxetine compared with placebo: 11/3455 (0.32%) versus 1/1978 (0.05%)."[43] A cohort study from Sweden recently showed an increase in violent crime in young adults taking antidepressants (hazard ratio 1.43, 95% confidence interval 1.19 to 1.73).[44]

Therefore we suggest minimal use of antidepressants in children, adolescents, and young adults, as the serious harms seem to be greater, and as their effect seems to be below what is clinically relevant.[4 45-47] Alternative treatments such as exercise[48 49] or psychotherapy[4 50] may have some benefit and could be considered, although psychotherapy trials also suffer from publication bias.[51]

The need for identifying hidden information in clinical study reports to form a more accurate view of the benefits and harms of drugs has been highlighted by the Restoring Invisible and Abandoned Trials (RIAT) initiative,[52] and the recent revised version of trial 329.[36] More data from clinical study reports are expected to become available in the coming years, with the EMA's new policy to make all newly submitted reports publicly available.[53] As it can be quite labour intensive to perform systematic reviews using clinical study reports, more reliable automated methods for text mining are needed, such that all data, including that from individual patient listings and case report forms, can be routinely considered.[36 54]

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Contributors: All authors had complete access to the data in the study. LSG was known by her maiden name Jensen at the time of the study. TS and PCG contributed to the study concept and design, wrote the protocol, and obtained funding. TS, LSG, and NF acquired the data for the study; all authors contributed to the analysis and/or interpretation of data. TS developed the first draft of the manuscript and all authors critically revised the manuscript and approved the final version. PCG is the study supervisor and guarantor.

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Transparency: The lead author (TS) and study guarantor (PCG) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspect of the study has been omitted. No discrepancies are withheld.

Data sharing: Additional data and the clinical study reports can be obtained from the corresponding author on request.

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Web extra material

Supplementary data A: additional details on methods
Supplementary data B: trial characteristics of included 70 randomised controlled trials
Supplementary data C: case notes for primary outcomes
Supplementary data D: additional analyses

5.2 Research article 2: Rare events meta-analysis methods

SharmaT, Gøtzsche PC, Kuss O. The Yusuf-Peto method was not a robust method for meta-anlayses of rare events data from antidepressant trials. *Journal of Clinical Epidemiology*, 2017 Aug 9. pii:S0895-4356.

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ORIGINAL ARTICLES

The Yusuf-Peto method was not a robust method for meta-analyses of rare events data from antidepressant trials

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Abstract

Objectives: The aim of the study was to identify the validity of effect estimates for serious rare adverse events in clinical study reports of antidepressants trials, across different meta-analysis methods.

Study Design and Setting: Four serious rare adverse events (all-cause mortality, suicidality, aggressive behavior, and akathisia) were meta-analyzed using different methods. The Yusuf-Peto odds ratio ignores studies with no events and was compared with the alternative approaches of generalized linear mixed models (GLMMs), conditional logistic regression, a Bayesian approach using Markov Chain Monte Carlo (MCMC), and a beta-binomial regression model.

Results: The estimates for the four outcomes did not change substantially across the different methods; the Yusuf-Peto method underestimated the treatment harm and overestimated its precision, especially when the estimated odds ratio deviated greatly from 1. For example, the odds ratio for suicidality for children and adolescents was 2.39 (95% confidence interval = 1.32–4.33), using the Yusuf-Peto method but increased to 2.64 (1.33–5.26) using conditional logistic regression, to 2.69 (1.19–6.09) using beta-binomial, to 2.73 (1.37–5.42) using the GLMM, and finally to 2.87 (1.42–5.98) using the MCMC approach.

Conclusion: The method used for meta-analysis of rare events data influences the estimates obtained, and the exclusion of double-zero event studies can give misleading results. To ensure reduction of bias and erroneous inferences, sensitivity analyses should be performed using different methods instead of the Yusuf-Peto approach, in particular the beta-binomial method, which was shown to be superior through a simulation study.

Keywords: Meta-analysis; Zero cells; Sparse data; Rare events; Method comparison; Beta-binomial method

1. Introduction

In order to provide a balanced assessment, systematic reviews should consider harms of treatments alongside benefits and their magnitude should be quantified [1]. Often adverse event data are handled with less rigor than the primary outcomes of a study in journal publications, and therefore, their monitoring needs careful scrutiny [2]. It has also become evident that inadequate power, poor research designs, and poor statistical analyses in combination with a high level of bias (including publication bias and selective reporting of clinical outcomes) make the majority of published literature unreliable [3,4].

Journal articles of antidepressant trials are highly selectively published, which was demonstrated by a study that compared the published literature for 12 antidepressants involving 12,564 patients with data belonging to the Food and Drug Administration (FDA). It found that among 74 FDA-registered trials, 31% were not published and the published trials were often those with positive results: 94% of the published trials appeared to be positive (statistically significant benefit of the primary outcome), in contrast to the complete FDA analysis, which showed that only 51% of the trials were in fact positive [5]. The revised publication of trial 329 of the antidepressant paroxetine using the clinical study report (CSR, detailed summary of trial results prepared by the drug industry for submission to regulatory authorities) [6] has also shown that the published article overestimated the benefit and underreported serious harms

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What is new?

Key findings

- Suicidality and aggressive behavior in children and adolescents has been underestimated previously using the Yusuf-Peto method. There are other more robust methods, for example, the beta-binomial model that can be employed for undertaking meta-analyses of rare events data and by using those we found higher odds of these serious adverse events.

What this adds to what was known?

- It is well established that meta-analyses of sparse data should employ different methods compared to meta-analysis of regular data, due to the existence of zero events in both groups in some trials. The Cochrane Collaboration recommends the use of the Yusuf-Peto method. If there is negligible difference between the two treatment arms, that is, the odds ratio is close to 1, then the Yusuf-Peto method can be considered to be robust. However, our current study along with previous research has suggested that when the estimated odds ratio deviates greatly from 1, this method is no longer reliable, as it underestimates the treatment harm and overestimates its precision. This is because it ignores studies that have null events in both arms (referred to as double-zero studies).

What is the implication and what should change now?

- We recommend that the Yusuf-Peto method should not be used in isolation for meta-analysis of sparse data. Methods that include the double-zero studies like the beta-binomial model could be considered superior and analyses with such methods should be undertaken.

like suicidal behavior [7]. Our previous research using CSRs of antidepressant trials showed that limitations in the study design and discrepancies in the reporting of these trials led to underreporting of serious harms [6].

For rare adverse events, meta-analyses may be the only way to obtain reliable evidence, as most individual studies are underpowered to detect differences in rare outcomes. A meta-analysis of multiple studies may bring adequate power to investigate whether the intervention impacts on the incidence of rare events. However, many standard methods for meta-analysis are based on large sample approximations and are unsuitable when events are rare [2]. The bias appears to be high with inverse variance, DerSimonian and Laird odds ratio or risk difference methods, and the Mantel–Haenszel (MH) odds ratio method when using a 0.5 zero-cell correction [8].

We recently undertook meta-analyses of serious rare adverse events using CSRs of 70 antidepressant trials using the Cochrane recommended Yusuf-Peto odds ratio method, due to the very low number of events [6]. This method has been shown to lead to unbiased estimates ‘‘when events are rare, treatment effects are small or moderate, and the numbers of treated and controlled participants are similar (balanced study design).’’ However, unbiasedness is only one aspect of valid statistical estimation, and we would also want estimates to come with correct standard errors. An additional disadvantage of the Yusuf-Peto approach is that it is only available for the odds ratio and not for absolute risk measures like the risk difference. Most important and as argued in our previous work, the implicit removal of double-zero studies limits the applicability of the Yusuf-Peto method [9]. Double-zero studies point to no differences in treatment effects, and removing them might bias the treatment effect away from the null [10]. With respect to ethics, patients who have been recruited to double-zero studies have a right that their data are included in meta-analyses [11]. We also cautioned against the use of continuity corrections, for example, adding 0.5 to each cell in the fourfold table of a double-zero study. This adds an unpleasant element of arbitrariness into the analysis [12] and, even worse, adds pseudoinformation that potentially yields too small standard errors of effect estimates resulting in over-optimistic findings. Using these practices (deletion of double-zero studies and adding pseudoinformation) is especially doubtful because alternative statistical methods are available and we compared them in a simulation study [9]. We were informed from this simulation that the beta-binomial model is a valid and reliable alternative for the meta-analysis of rare events, which avoids the above-mentioned problems.

In the following, we assess the robustness of our previous Yusuf-Peto results by comparing them to the results of more recent statistical methods.

2. Methods

The compared methods are those used previously by the FDA [13], Gunnell et al. [14], and other methods that allow for the incorporation of double-zero studies such as the beta-binomial method. [9,15] When the FDA reported on suicidality, they used a fixed effect model (MH) and a random effects model (DerSimonian–Laird) for their meta-analyses, with a continuity correction of 0.5 for trials with events in one group and no events the other. They excluded trials with no events [13]. Both methods have been consistently shown to be highly unreliable and biased [8,9], and we will therefore not use these methods. Our rare outcomes were all-cause mortality, suicidality (suicide, suicide attempt or preparatory behavior, intentional self-harm,

and suicidal ideation), aggressive behavior, and akathisia, taken from our systematic review of 70 antidepressant trials [6]. All analyses were conducted using SAS, version 9.4 (SAS Inc., Cary, NC). In the following, we describe the statistical methods; briefly, some additional statistical details are given in Supplementary Document A at www.jclinepi.com.

2.1. Yusuf-Peto's odds ratio

This method was first introduced in 1985 and has become the method of choice for rare events [16]. In meta-analyses, the relative weights given to individual trials are determined by the variance of the effect measure used and the variance of a trial is calculated from the underlying risk, which is estimated from data [17]. This method gives zero weight to trials with no events and so effectively excludes them from the analysis [8].

This was the original method we used for the analysis of the outcomes [6], and we therefore essentially excluded trials with no events. Our previous estimates will be given here to compare them to the values obtained by the other methods listed below.

2.2. Generalized linear mixed models

A meta-analysis with binary outcomes can be perceived as a generalized linear mixed model (GLMM) with a binary outcome, the treatment as a fixed effect, and a normally distributed random intercept term for the study [9]. This method uses a random study effect that allows for the possibility that outcomes of patients within a single study might be correlated and that baseline event probabilities between studies might be different, as long as they follow a normal distribution across studies. By changing the link function from the canonical logit link (which gives an estimated log odds ratio for the treatment effect), we can also obtain estimates for the log relative risk (by using the log link) or the risk difference (by using the identity link) [9]. There are a number of estimation methods for GLMMs, which is due to the complexity of the model's likelihood function that includes integrals, which cannot be solved analytically. We use the approximative penalized quasilikelihood (PQL) method here, which is implemented in the GLIMMIX procedure in SAS.

2.3. Conditional logistic regression

The FDA also undertook analyses using conditional logistic regression [13]. This method can also be used to pool binary outcomes from multiple studies, and the numbers of events in the study arms are modeled using binomial distributions [18]. The correlation of patients within studies is accounted for by conditioning out the study effect from the model's likelihood function. This avoids assuming a distribution for the random intercept effect as in the GLMM. The conditional likelihood function that is obtained by this process is equivalent to the partial likelihood function from a Cox proportional hazard model. In its original form, it does not include double-zero studies, but by using the robust sandwich estimate (COVSANDWICH statement in the PHREG procedure) of Lin and Wei (1989), these studies can be included [9].

2.4. Bayesian approach

The UK regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), used a Bayesian random effects model to synthesize data across their three outcomes of suicidal behavior [14]. Actually, the underlying statistical model is identical to the GLMM; however, the estimation method is different. By using the idea of Markov Chain Monte Carlo (MCMC), we address the integrals in the model's likelihood by stochastic simulation and achieve parameter estimates from the posterior distribution. In the Bayesian context, it is necessary to give prior distributions for the parameters and we followed the MHRA's approach of giving noninformative priors [N (0, 10,000) for the intercept and the treatment effect and inverse gamma (0.01, 0.01) for the random effects variance].

2.5. Beta-binomial

The beta-binomial method is another method for logistic regression with correlated responses, and it is also a random effects model. However, the beta-binomial model comes with the advantage that the model has a closed form likelihood function and was seen to yield convergence also in very challenging situations with a very low number of events or studies. Analogous to a GLMM and conditional logistic regression, the beta-binomial models assume binomial distributions for the events in the treatment arms but allows for the event probability across studies in the control arms to follow a beta-distribution [9]. The events in treatment arms of studies are then linked to the control arms by a simple regression equation with an appropriate link function, in our case the standard logit link.

2.6. Standard errors

As seen in our previous work [9], standard errors from methods that ignore studies with zero cells or add pseudoobservations to deal with them were frequently too small. This is no surprise because both tactics effectively enhance the overall sample size. We therefore also report estimation variances (the square of the estimated standard error) for each estimate relative to the estimation variance of the Yusuf-Peto method. Using the variances instead of the more commonly reported standard errors has the advantage that these are inversely proportional to the sample size. As such, a variance from a beta-binomial model, which is 50% larger than that from the Yusuf-Peto (yielding a ratio of 1.5), would mean that the Yusuf-Peto method pretends that it had 50% more observations than the beta-binomial model.

3. Results

As stated before, the data sets used for this study were taken from a review of serious adverse effects of newer antidepressants that included 70 trials [6]. For each of the four outcomes, we compared the level of sparseness (number of null events) of the data, and this is described in Table 1. One can see that for certain outcomes (all-cause mortality: adults and akathisia: adults), the percentage of double-zero studies is more than 80%, and ignoring this information with the Yusuf-Peto method seems highly inappropriate. We then conducted the meta-analyses using the five different methods for the four rare outcomes and compared the resulting odds ratios, standard errors, and variances (see Table 2 and Figs. 1–4 and Supplementary Data Document B at www.jclinepi.com).

Our original estimate for all-cause mortality (only seen in adults) with the Yusuf-Peto method was odds ratio (OR) = 1.28; 95% confidence interval (CI) = 0.40–4.06. Using the different methods, this value ranged from 1.37 (95% CI = 0.42–4.49) using the GLMM-PQL method to 1.51 (95% CI = 0.47–5.52) using the Bayesian approach (GLMM-MCMC), which is a fairly big variation (see Table 2 and Fig. 1). Therefore, when we compare the values, the original estimate using the Yusuf-Peto method gives us the lowest value and the lowest variance, underestimating both the size and the uncertainty of treatment harm. The highest value for the estimate and variance was seen with the Bayesian method, while all other estimates were in between. Our original odds ratio from the Yusuf-Peto method for suicidality for adults was 0.81 (95% CI = 0.51–1.28), and the subsequent estimates using the different methods ranged from 0.83 (95% CI = 0.53–1.30) using the GLMM-PQL method to 0.94 (95% CI = 0.52–1.70) using the beta-binomial method, following a similar pattern (see Table 2 and Supplementary Data Document B at www.jclinepi.com).

If we consider the outcome of suicidality in children and adolescents, the range for the odds ratio seen here was 2.39 (95% CI = 1.32–4.33, using the Yusuf-Peto method) to 2.87 (95% CI = 1.42–5.98, using the Bayesian: GLMM-MCMC approach, see Fig. 2 and Table 2). So, the Yusuf-Peto odds ratio underestimated the treatment effect by about 10% (OR = 2.39 vs. 2.64 if we consider the next lowest value obtained via the logistic regression method), but it simultaneously overestimates the precision by 33%, that is, it pretends to have a third more observations than it actually has. Taking a public health perspective and going

Table 1. Description of sparseness across the data for the four outcomes

Sparse	Frequency	Percentage	Cumulative frequency	Cumulative percentage
All-cause mortality, adults				
Regular (no zero studies)	2	3.5	2	3.5
Single-zero treatment	2	3.5	4	7.0
Single-zero control	5	8.8	9	15.8
Double zero	48	84.2	57	100.0
Suicidality, adults				
Regular (no zero studies)	12	21.1	12	21.1
Single-zero treatment	7	12.3	19	33.3
Single-zero control	11	19.3	30	52.6
Double zero	27	47.4	57	100.0
Suicidality, children and adolescents				
Regular (no zero studies)	6	54.5	6	54.6
Single-zero treatment	1	9.1	7	63.7
Single-zero control	4	36.4	11	100.0
Aggressive behavior, adults				
Regular (no zero studies)	5	8.8	5	8.8
Single-zero treatment	4	7.0	9	15.8
Single-zero control	13	22.8	22	38.6
Double zero	35	61.4	57	100.0
Aggressive behavior, children and adolescents				
Regular (no zero studies)	5	45.5	5	45.5
Single-zero treatment	1	9.1	6	54.6
Single-zero control	5	45.5	11	100.0
Akathisia, adults				
Regular (no zero studies)	1	1.7	1	1.7
Single-zero treatment	1	1.7	2	3.5
Single-zero control	8	13.8	10	17.2
Double zero	48	82.8	58	100.0
Akathisia, children and adolescents				
Regular (no zero studies)	1	9.1	1	9.1
Single-zero treatment	1	9.1	2	18.2
Single-zero control	2	18.2	4	36.4
Double zero	7	63.6	11	100.0

Table 2. Effect estimates and other statistical parameters using the different methods for the four outcomes

Outcome and method	Odds ratio (OR) (95% confidence intervals)	Standard error of log OR	Variance of log OR
All-cause mortality, adults			
Yusuf-Peto	1.28 (0.40–4.06)	0.5906	0.3488
Generalized linear mixed model (GLMM-PQL)	1.37 (0.42–4.49)	0.6051	0.3662
Conditional logistic regression	1.29 (0.39–4.29)	0.6139	0.3768
Bayesian approach (GLMM-MCMC)	1.51 (0.47–5.52)	0.6469	0.4185
Beta-binomial	1.33 (0.39–4.49)	0.6211	0.3858
Suicidality, adults			
Yusuf-Peto	0.81 (0.51–1.28)	0.2344	0.0549
Generalized linear mixed model (GLMM-PQL)	0.83 (0.53–1.30)	0.2268	0.0515
Conditional logistic regression	0.81 (0.52–1.27)	0.2299	0.0528
Bayesian approach (GLMM-MCMC)	0.83 (0.53–1.31)	0.2303	0.0531
Beta-binomial	0.94 (0.52–1.70)	0.2998	0.0899
Suicidality, children and adolescents			
Yusuf-Peto	2.39 (1.32–4.33)	0.3041	0.0925
Generalized linear mixed model (GLMM-PQL)	2.73 (1.37–5.42)	0.3502	0.1226
Conditional logistic regression	2.64 (1.33–5.26)	0.3515	0.1236
Bayesian approach (GLMM-MCMC)	2.87 (1.42–5.98)	0.3562	0.1269
Beta-binomial	2.69 (1.19–6.09)	0.4164	0.1734
Aggressive behavior, adults			
Yusuf-Peto	1.09 (0.55–2.14)	0.3452	0.1191
Generalized linear mixed model (GLMM-PQL)	0.95 (0.49–1.86)	0.3416	0.1167
Conditional logistic regression	1.09 (0.55–2.15)	0.3469	0.1204
Bayesian approach (GLMM-MCMC)	0.97 (0.50–1.91)	0.3390	0.1149
Beta-binomial	1.15 (0.52–2.55)	0.4046	0.1637
Aggressive behavior, children and adolescents			
Yusuf-Peto	2.79 (1.62–4.81)	0.2775	0.0770
Generalized linear mixed model (GLMM-PQL)	3.01 (1.60–5.67)	0.3224	0.1040
Conditional logistic regression	3.12 (1.66–5.88)	0.3229	0.1043
Bayesian approach (GLMM-MCMC)	3.02 (1.66–5.77)	0.3314	0.1098
Beta-binomial	2.92 (1.26–6.78)	0.4301	0.1850
Akathisia, adults			
Yusuf-Peto	2.00 (0.79–5.04)	0.4720	0.2227
Generalized linear mixed model (GLMM-PQL)	2.35 (0.78–7.08)	0.5617	0.3155
Conditional logistic regression	2.24 (0.74–6.79)	0.5649	0.3191
Bayesian approach (GLMM-MCMC)	2.61 (0.90–9.72)	0.5576	0.3109
Beta-binomial	3.60 (0.78–16.67)	0.7815	0.6107
Akathisia, children and adolescents			
Yusuf-Peto	2.15 (0.48–9.65)	0.7666	0.5876
Generalized linear mixed model (GLMM-PQL)	2.28 (0.44–11.8)	0.8408	0.7069
Conditional logistic regression	2.27 (0.43–11.9)	0.8443	0.7129
Bayesian approach (GLMM-MCMC)	2.72 (0.53–19.6)	0.9470	0.8968
Beta-binomial	1.60 (0.27–9.56)	0.9108	0.8296

Abbreviations: GLMM, generalized linear mixed models; MCMC, Markov Chain Monte Carlo; PQL, penalized quasilikelihood.

to absolute numbers, these differences are far from being trivial. Attempted suicide has been noted to be the most common cause of hospital admissions in young people, and suicide is among the most common causes of death in this age group. For example, in 2009, the annual rate of attempted suicides was 300 per 100,000 in Denmark [19]. As the number of 15- to 24-year-old young people in Denmark in 2016 (second quarter) is about 740,000, this equates to approximately 2,220 suicidal attempts per year [20]. Assuming a 5% treatment prevalence with antidepressants, we would expect 110 suicidal attempts under placebo, 263 under treatment from the Yusuf-Peto odds ratio, but 296 from the beta-binomial model. That is, using the Yusuf-Peto estimate, we would miss, only in Denmark, 33 suicidal attempts per year.

Similar trends were seen for the remaining outcomes. For aggressive behavior, the Yusuf-Peto odds ratio was 1.09 (95% CI = 0.55–2.14) for adults and 2.79 (95% CI = 1.62–4.81) for children and adolescents, with other methods it ranged from 0.95 (95% CI = 0.49–1.86) to 1.15 (95% CI = 0.52–2.55) and from 2.92 (95% CI = 1.26–6.78) to 3.12 (95% CI = 1.66–5.88), respectively. For akathisia, the Yusuf-Peto odds ratio was 2.00 (95% CI = 0.79–5.04) for adults and 2.15 (95% CI = 0.48–9.65) for children and adolescents, with other methods it ranged from 2.24 (95% CI = 0.74–6.79) to 3.60 (95% CI = 0.78–16.67) and 1.60 (95% CI = 0.27–9.56) to 2.72 (95% CI = 0.53–19.58), respectively (see Table 2, Figs. 3 and 4 and Supplementary Data Document B at www.jclinepi.com).

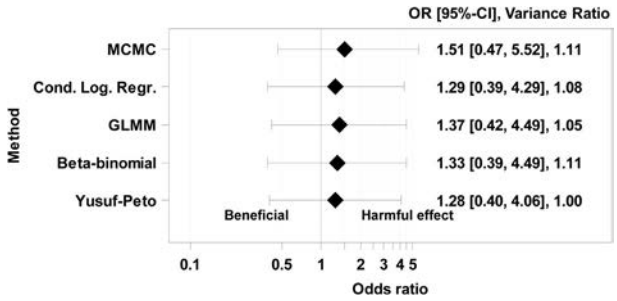

Fig. 1. Comparison of odds ratio estimates using the different methods for all-cause mortality (adults). CI, confidence interval; OR, odds ratio; MCMC, Markov Chain Monte Carlo (Bayesian approach); Cond. Log. Regr., conditional logistic regression; GLMM, generalized linear mixed model (using the penalized quasilikelihood).

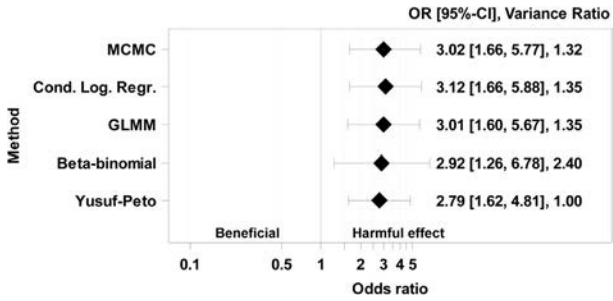

Fig. 3. Comparison of odds ratio estimates using the different methods for aggressive behavior (children and adolescents). CI, confidence interval; OR, odds ratio; MCMC, Markov Chain Monte Carlo (Bayesian approach); Cond. Log. Regr., conditional logistic regression; GLMM, generalized linear mixed model (using the penalized quasilikelihood).

In general, when the odds ratio is close to 1, the Yusuf-Peto method gives similar estimates as the other methods. However, if the estimate deviates from 1, the Yusuf-Peto odds ratio underestimates the treatment effect and gives a smaller variance, thus underestimating the statistical uncertainty.

4. Discussion

Undertaking meta-analyses of sparse data has several challenges, and it is therefore essential to identify the most appropriate method to avoid getting biased estimates and overoptimistic findings due to too small estimation variances. Our previous work has shown that the recommend Yusuf-Peto method ignores double-zero studies, and other methods such as the beta-binomial method were found to be either comparable or superior in terms of convergence, empirical power, and empirical coverage [9].

This study confirms these findings in a sample of adverse events data in antidepressant trials. The four outcomes under study had many instances of single-zero studies, as well as double-zero studies and represent a good example of sparse data often seen for serious adverse events. The outcomes also varied in terms of treatment effect, such that we could see where the real problems lie with the Yusuf-Peto method and where it can be especially problematic. Our study demonstrates that when there is no treatment effect (the odds ratio is close to 1), the odds ratio obtained using the Yusuf-Peto method coincides well with the other methods in both aspects, with respect to the value of the estimate and with respect to precision (variance ratio near 1). However, when the odds ratio deviates from 1, the Yusuf-Peto odds ratio underestimates the effect and also comes with a remarkably higher precision which is actually a misleading pseudoprecision that arises from the excluded double-zero studies and/or the continuity corrections applied.

As we have suggested earlier, the Cochrane recommended Yusuf-Peto method can be improved upon [9], and therefore, we recommend that other statistical methods that allow for the inclusion of double-zero studies should be employed, either as the primary analysis method or in the form of sensitivity analyses, for meta-analyses of rare events. Our study and our previous work suggest that the beta-binomial method tends to either be comparable or outperform the Yusuf-Peto method and could be a suitable candidate for the method of choice for rare events meta-analyses [9]. While this previous recommendation was a

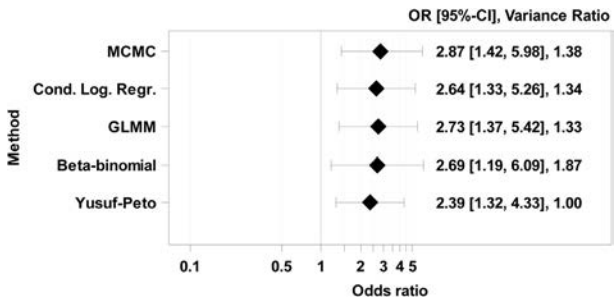

Fig. 2. Comparison of odds ratio estimates using the different methods for suicidality (children and adolescents). CI, confidence interval; OR, odds ratio; MCMC, Markov Chain Monte Carlo (Bayesian approach); Cond. Log. Regr., conditional logistic regression; GLMM, generalized linear mixed model (using the penalized quasilikelihood).

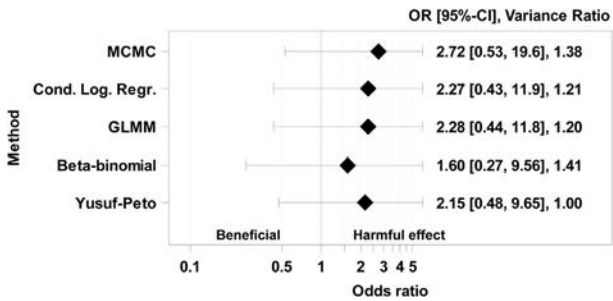

Fig. 4. Comparison of odds ratio estimates using the different methods for akathisia (children and adolescents). CI, confidence interval; OR, odds ratio; MCMC, Markov Chain Monte Carlo (Bayesian approach); Cond. Log. Regr., conditional logistic regression; GLMM, generalized linear mixed model (using the penalized quasilikelihood).

quite general one that was averaged across a number of simulations scenarios (which differed with respect to the proportion of double-zero studies, the size of the treatment effect, the number of studies per meta-analysis, the sample size of the single studies, and the random effects variance), it should be acknowledged that there might be specific situations where some other method would be preferable over the beta-binomial model. As such and to gain an impression how the results might be for the specific situations in our paper, we rerun our simulation study mimicking the observed data sets for our seven outcomes and report the design of the study and the results in Supplementary Data Document C at www.jclinepi.com. Briefly, the Yusuf-Peto method worked well when simulation data were generated from a fixed-effects model, but the beta-binomial model was superior, especially with respect to empirical coverage, when true data were generated from a random effects model. That is, our recommendation that the beta-binomial model can be used for rare events meta-analysis is valid also for the specific situation here.

The MCMC method often gives the largest confidence intervals, and on peer review, it was conjectured that could be due to noninformative prior distributions for all parameters chosen in the analyses. We therefore checked the sensitivity of the MCMC estimates against prior specification by using additionally a semiinformative and an informative prior scenario (details are available on request), and indeed, the length of CIs got smaller with an increasing ''informativity'' of the prior distributions. That means that analyses for other data sets by MCMC methods might benefit (with respect to statistical power) by a carefully chosen informative prior distribution as they are given, for example, in the two papers of Turner et al. [21,22].

Due to the difference in values seen based on the method employed for suicidality and aggressive behavior in children and adolescents (as the values deviate greatly from 1), one can infer that our original paper that used the Yusuf-Peto method underestimated the potential harm and overestimated precision of estimates. A previous systematic review that considered these newer antidepressants for depressive disorders in children and adolescents found an increased risk (58%) of suicide-related outcomes for the drugs compared to placebo (17 trials; $N = 3{,}229$; relative risk was 1.58; 95% CI = 1.02–2.45) [23]. However, this review employed the MH method with the 0.5 correction and a random effects model, which is even less reliable than the Yusuf-Peto method [8,18] and can also give underestimates. It is therefore quite likely that the harm caused by these newer antidepressants for children and adolescents is even greater than we previously reported [6], and therefore, we suggest that safer treatments should be offered to this age group such as psychotherapy and exercise [24,25].

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jclinepi.2017.07.006.

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5.3 Research article 3: Comparative study drop-out rates

Sharma T, Guski LS, Freund N, Meng DD, Gøtzsche PC. Drop-outs rates in placebo-controlled trials of antidepressant drugs: systematic review and meta-analysis based on clinical study reports. ***(Submitted)***

Drop-out rates in placebo-controlled trials of antidepressant drugs: systematic review and meta-analysis based on clinical study reports

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Keywords: selective serotonin reuptake inhibitors; serotonin-norepinephrine reuptake inhibitors; drop-out rates; drug acceptability; drug tolerability, clinical study reports

Abstract: 415 words
Manuscript: 3169 words
Tables: 1
Figures: 4
References: 31
Supplementary Document A – Glossary of terms and additional details on methods
Supplementary Document B – Additional tables and figures and Sensitivity analyses using beta-binomial method for secondary outcomes
Supplementary Document C – Funnel plots for the primary and secondary outcomes

ABSTRACT

Objective: To study the drop-out rates in trials of selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs).

Design and setting: Systematic review and meta-analysis of trials.

Main outcome measure: Overall drop-out rate. Secondary outcomes were drop-outs due to adverse events and lack of effect.

Data sources: Clinical study reports (CSRs) of five antidepressant drugs obtained from the European Medicines Agency and the UK's Medicines and Healthcare products Regulatory Agency.

Eligibility criteria for selecting studies: Double-blind randomised, placebo-controlled trials for any indication.

Data extraction and analysis: The primary outcome was extracted by two researchers independently and meta-analysed using the Mantel-Haenszel method (fixed effect model). The secondary outcomes were extracted by one researcher and checked by another. Sensitivity analyses were performed using Peto's odds ratio and beta binomial methods, due to presence of null events, and by excluding unreliable trials.

Results: We included 71 CSRs (67,319 pages) with information on 73 trials (11,057 patients on SSRI or SNRI drugs, and 7,369 on placebo). There were minor discrepancies within the CSRs when a modified intention to treat principle was used and patients lost to follow up early in the trial were not accounted for. Significantly more patients dropped out on active drug than on placebo, risk ratio 1.08 (95% CI 1.03 to 1.13), with no difference between adults and children/ adolescents, RR = 1.08 (1.03 to 1.13) and 1.07 (0.95 to 1.21), respectively. When three trials with a prior single-blind phase on active drug were removed, the difference was a risk ratio of 1.12 (1.07 to 1.18), whereas the result was the same after removal of three trials with fraudulent data or other issues with data validity, risk ratio 1.08 (1.03 to 1.13). There were more drop-outs due to adverse events on active drug than on placebo, risk ratio 2.63 (2.33 to 2.96). There were fewer drop-outs due to lack of effect, risk ratio 0.47 (0.43 to 0.53). However, this result is biased; when more people drop out due to adverse effects, fewer can drop out because of lack of effect.

Conclusions: By using CSRs, we were able to demonstrate for the first time that more patients dropped out on active drug than on placebo. As it can be argued that the drop-out rate reflects the patients' overall assessment of the balance between benefits and harms, our review adds to the growing concern that SSRIs and SNRIs might not have the desired effect. Our review also highlights the importance of using CSRs for undertaking reviews of drugs.

INTRODUCTION

The consequences of publication bias and other types of selective reporting have finally come to the forefront of clinical research. Only about half of all studies presented as abstracts are subsequently published[1] and trials primarily sponsored by industry are less likely to be published than non-industry/ non-government sponsored trials (risk ratio [RR] = 0.73, 95% confidence interval [CI] 0.61 to 0.87).[2] Due to the seriousness of this problem, there has been a push for transparency,[3,4] and a move towards using clinical study reports (CSRs) for systematic reviews rather than journal articles to reduce bias. CSRs are comprehensive documents containing the results of trials prepared by the drug industry for submissions to regulatory authorities for getting marketing authorisation. CSRs contain important information that does not exist in published articles,[5-9] e.g. we have shown that antidepressants more than double the occurrence of aggression in children and adolescents.[8] We have also shown that activation events (defined by the FDA as, for example, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania),[10] were four times more common with duloxetine than with placebo in trials in women with stress urinary incontinence, (RR = 4.45, 3.22 to 6.14).[7] Others have shown based on CSRs that the benefit of neuraminidase inhibitors for influenza is doubtful.[5]

In trials of antidepressants, relatively objective outcomes such as suicide attempts, hospital admissions, job loss or dropping out of the trial are considered more reliable and relevant than subjective scores on a ranking scale.[11] Drug acceptability by patients is a vital component of treatment effectiveness and the overall study drop-out rates have been used successfully to measure acceptability for many years.[12-16] Drop-out rates have also been used as performance indicators for psychotherapy, where high attrition rates are a proxy for ineffective service delivery.[17] Studying drop-outs due to adverse events might give an indication of the tolerability of a drug,[11,12] while studying drop-outs due to lack of effect[13] can be more problematic. If a drug gives many adverse effects (often occurring early after the administration of the drug) and if these lead to many drop-outs, there will be few who can drop out because of lack of effect.

We report here, using data from CSRs, overall study drop-outs (acceptability), drop-outs due to adverse events (tolerability) and drop-outs due to lack of effect, of selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRI and SNRI, respectively) in placebo-controlled trials.

METHODS

Data access

We requested access to the CSRs for all placebo-controlled randomised trials (RCTs) for SSRIs and SNRIs from the European Medicines Agency (EMA), irrespective of indication. As fluoxetine was first approved in the UK, EMA did not have the relevant documents, which we requested from the UK's Medicines and

Healthcare products Regulatory Agency (MHRA). We did not get access to the CSRs for all the relevant trials for all the relevant drugs and therefore conducted the review based on the SSRI or SNRI trials we received and that fulfilled our inclusion criteria. Further details are available in our previous publication[8] and supplementary document A.

Data selection and outcomes

We included all double-blind placebo controlled RCTs that were not healthy volunteer studies or cross-over trials and that contained results for study drop-outs. As explained previously,[8] the scanned PDF documents were converted to a text-recognisable format by one researcher (TS) and all relevant pages with outcome data, both tables and text, were extracted. Most of the data on study information had previously been extracted for our review of serious harms.[8] Study information data on additional trials was extracted by one researcher (TS). The primary outcome was the overall (all-cause) drop-out rate (acceptability of the drug)[13,15-16,18] which was independently extracted by two researchers (TS plus LSG, NF or DMM). The secondary outcomes were drop-out rate due to adverse events (tolerability of the drug)[18] and due to lack of effect; they were extracted by one researcher (TS) and checked by another (DMM).

Analyses

We conducted meta-analyses comparing SSRIs or SNRIs with placebo for all indications. For trials with more than one active intervention arm, we combined the data for all SSRI and SNRI drugs together. We included all events that occurred after randomisation including the lead-out phase when such information was available but did not include events in an extension phase. For the secondary outcome of drop-out due to adverse events (tolerability), where data was split in the drug arm into 'not related to the drug' or 'possibly related to the drug' or equivalent, we combined the data. For the secondary outcome of drop-out due to lack of effect, where data was split into 'patient' and 'physician perception', or equivalent, we combined the data.

The data was meta-analysed with the Mantel-Haenszel method (fixed effect model; RevMan 5.3) and we report risk ratios (RR) with 95% confidence intervals (CI). Subgroup analyses were done based on the age of the study participants (adults or children and adolescents) as age-related effects were seen in our first review.[8] One study (S-7, which means sertraline trial 7), which had a study population of people between 16 and 75 years, was included in the adult subgroup.

Sensitivity analyses were done for the primary outcome by removing three trials that had a single-blind phase on study drug prior to randomisation (D-11, P-1 and P-5) and by removing three trials with fraudulent data or other issues with data validity (P-7, P-10 and V-6) as suggested by the peer reviewers of our first review.[8]

Post-hoc sensitivity analyses, not described in our protocol for the review, were done for the secondary outcomes using Peto's odds ratio and the beta-binomial odds ratio due to the presence of null events in some trials.[19,20] The beta-binomial odds ratio was analysed using SAS 9.4 adapting the code developed and used in our previous research. [20] We collated the data for other active comparators as per our protocol but did not conduct any meta-analyses as we had not asked the drug regulators for CSRs on other types of antidepressants than SSRIs and SNRIs. Details of the methods and glossary of terms used within the clinical study reports are available in supplementary document A.

Patient involvement

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. However, we will try to involve patient organisations in the dissemination of our results.

RESULTS

We got access to 198 CSRs, which included 125 non-relevant trials (they were not RCTs, or were cross-over RCTs or healthy volunteer studies and two CSRs had unusable data on drop-out rates, see Figure 1). We included 71 CSRs (67,319 pages) that had information on drop-outs in 73 trials, regardless of the indication. There were 23 trials of duloxetine (D-1 to D-23, all the same as in our previous review), three trials of fluoxetine (F-1 to F-3, as in our previous review), 10 trials of paroxetine (P-1 to P-10; we added two additional studies, P-1 and P-5), 29 trials of sertraline (S1 to S-29; one additional study S-15) and eight trials of venlafaxine or venlafaxine extended release (V-1 to V-8, as in our previous review). For two pairs of sertraline trials (S-9 and S-10; and S-13 and S-14); the results had been combined into a single CSR and separating the results data was not possible.

There were 62 trials in adults with 16,999 patients (9,897 on SSRI or SNRI drugs, 757 on other active comparators and 6,345 on placebo) and 11 paediatric trials with 2,279 patients (1,160 on SSRI or SNRI drugs, 95 on imipramine and 1,024 on placebo). In total, 19,278 patients (11,057 on SSRI or SNRI drugs, 852 on other active comparators and 7,369 on placebo). For trial D-1, the CSR had results only till an interim analysis when the total population was 105 patients (53 on duloxetine and 52 on placebo), whereas the plan was to recruit at least 132 patients. The main trial characteristics are summarised in supplementary document B.

There were serious problems with the trial design, which we have discussed in detail in our previous review.[8] One issue was having a short placebo lead-in period and only randomising those patients who did not improve on placebo. Having a short wash-out phase for patients previously treated with similar drugs meant that some patients randomised to placebo had withdrawal effects, which can be long-lasting.[21] Another issue

was that the use of minor tranquilizers was permitted in 71% of the trial protocols for insomnia, which is a known adverse effect of antidepressant drugs.[22,23] Differential use of such sedatives could therefore have biased the trials. As stated in the methods section, there were three trials (D-11: duloxetine trial protocol HMBC; P-1 and P-5: paroxetine trial protocols 595 and 646) that had a single-blind phase on SSRI or SNRI (of 12, 8 and 12 weeks, respectively) prior to the double-blind randomised phase, misleadingly called an "enriched" design. This meant that only those patients that had tolerated the drug were randomised.

There were also issues with data handling and reporting. Fraud and other concerns with the validity of data occurred in four centres in three trials, and the reporting of the results in the CSRs was of varying quality.[8]

The companies had often analysed the data using a modified intention-to-treat (ITT) principle where study participants with missing data on benefits or harms were not included in the analyses. We have included these patients as drop-outs, as we could identify them in the study reports.

Acceptability: overall study drop-outs

Data on the number of study drop-outs during the placebo lead-in phase was only available in 29 of the 73 trials and in the lead-out phase only in 20 trials. There were 5,560 study drop-outs (30%) post-randomisation among the 18,426 patients in all arms. Significantly more patients dropped out on SSRIs or SNRIs than on placebo, RR = 1.08 (1.03 to 1.13, see Figure 2), with no difference between adults and children/ adolescents, RR = 1.08 (1.03 to 1.13) and 1.07 (0.95 to 1.21), respectively. There was considerable heterogeneity, I^2 = 67%. The funnel plot (see supplementary document C) looked symmetrical despite the high heterogeneity, however, indicating limited reporting bias.

When the three trials with a prior single-blind phase on SSRI or SNRI, were removed, the difference was more pronounced, RR = 1.12 (1.07 to 1.18) and the heterogeneity was a bit less (I^2 =58%), whereas the result was the same after removal of the three trials with fraudulent data or other issues with data validity, RR = 1.08 (1.03 to 1.13) with similar heterogeneity as before I^2 = 68% (see supplementary document B, figures 1a and 1b respectively).

Additionally, there were 426 study drop-outs on other active comparator drugs in eight trials (63 on amitriptyline in 149 patients, 110 on clomipramine in 217 patients, 24 on desipramine in 45 patients, 144 on imipramine in 364 patients and 28 on trazodone in 77 patients). All but one of these trials were in adults, with 331 events in 757 patients. The trial in children and adolescents (P-6) had 38 events on imipramine in 95 patients.

Tolerability: study drop-outs due to adverse events

There were 1,634 study drop-outs due to adverse events among the 18,426 patients post randomisation. Significantly more patients dropped out on SSRIs or SNRIs than on placebo, RR = 2.63 (2.33 to 2.96, see Figure 3), with similar risk ratios in adults and children/ adolescents, 2.66 (2.34 to 3.02) and 2.38 (1.67 to 3.39), respectively. There was little heterogeneity, I^2 = 36%. The funnel plot of the data (see supplementary document C) was not as symmetrical as for the primary outcome but still indicated limited reporting bias.

As there were three trials with null events in one arm (F-3, S-9 and S-10, and S-27), we also did sensitivity analyses using Peto's odds ratio and the beta-binomial method, which showed similar results, odds ratio 2.55 (2.29 to 2.85) and 2.57 (2.06 to 3.20), respectively (see supplementary document B, figure 2 and section 2A).

There were additionally 155 study drop-outs due to adverse events across the 852 patients on other active comparators (28 on amitriptyline in 149 patients, 24 on clomipramine in 85 patients, 13 on desipramine in 45 patients, 72 on imipramine in 364 patients and 18 on trazodone in 77 patients). All but one of these were trials in adults with 125 events in 757 patients. The trial in children and adolescents (P-6) had 30 events on imipramine in 95 patients.

Study drop-outs due to lack of effect

Four trials (D-19, D-20, D-22 and S-28) did not have data for this outcome. There were 1,336 study drop-outs due to lack of effect among the 17,767 patients randomised. Significantly fewer patients dropped out on SSRIs or SNRIs than on placebo due to lack of effect, RR = 0.47 (0.43 to 0.53, see Figure 4), with similar risk ratios in adults and children/ adolescents, 0.46 (0.41 to 0.52) and 0.54 (0.41 to 0.72), respectively. There was little heterogeneity, I^2 = 5%. The funnel plot of the data indicated limited reporting bias (see supplementary document C).

As there were three trials with null events in one arm (D-15 and D-18, S-21) and one trial with null events in both arms (S-22), we also did sensitivity analyses using Peto's odds ratio and the beta-binomial method, which showed similar results, 0.40 (0.37 to 0.48) and 0.56 (0.42 to 0.74), respectively (see supplementary document B, figure 3 and section 2B).

There were additionally 26 study drop-outs due to lack of effect across the 852 patients on other active comparators (six on amitriptyline in 149 patients, four on clomipramine in 85 patients, two on desipramine in 45 patients, six on imipramine in 364 patients and three on trazodone in 77 patients). All but one of these were trials in adults with 25 events in 757 patients. The trial in children/ adolescents (P-6) had one event on imipramine in 95 patients.

Table 1: The meta-analysis results for the primary and secondary outcomes

Outcome	Analysis method	Effect estimate	95% Confidence interval
Overall drop-outs (acceptability)	Mantel-Haenszel	RR=1.08	1.03 to 1.13
	Sensitivity analyses 1	RR=1.12	1.07 to 1.18
	Sensitivity analyses 2	RR=1.08	1.03 to 1.13
Drop-outs due to adverse events (tolerability)	Mantel-Haenszel	RR=2.63	2.33 to 2.96
	Sensitivity analyses 3	OR=2.55	2.29 to 2.85
	Sensitivity analyses 4	OR=2.57	2.06 to 3.20
Drop-outs due to lack of effect	Mantel-Haenszel	RR=0.47	0.43 to 0.53
	Sensitivity analyses 3	OR=0.40	0.37 to 0.48
	Sensitivity analyses 4	OR=0.56	0. 42 to 0.74

Sensitivity analysis 1: done for the acceptability by removing three trials that previously had a single-blind phase with the study drug prior to randomised phase (D-11, P-1 and P-5)
Sensitivity analysis 2: done for the acceptability by removing three trials with fraudulent data or issues with data validity (P-7, P-10 and V-6)
Sensitivity analysis 3: done for tolerability and drop-outs due to lack of effect using the Peto's odds ratio method
Sensitivity analysis 4: done for tolerability and drop-outs due to lack of effect using the beta binomial method
RR: risk ratio; OR: odds ratio

DISCUSSION

We found that significantly more patients dropped out of the trials when they received an SSRI or SNRI than when they received placebo. In the sensitivity analysis, where we excluded three trials that had a single-blind run-in phase of 8 to 12 weeks on an SSRI or SNRI and only patients who tolerated the drug were randomised ("enriched" design, which is prone to give biased results), we found that 12% more patients dropped out when they received an SSRI or SNRI than when they received placebo. Our result confirms the importance of working with CSRs when conducting systematic reviews of drugs, as our finding is unique: previous reviews using mostly published data failed to find more drop-outs on active drugs,[11,24] e.g. a large review of 40 trials (6391 patients) reported RR = 0.99 (0.88 to 1.11) when paroxetine was compared with placebo.[11] A third previous review focused on palliative care patients and found no difference in overall drop-outs after short-term follow-up, but at 9-18 weeks, fewer patients receiving placebo had withdrawn than those treated with antidepressants (SSRIs or tricyclic antidepressants, odds ratio 2.09 (1.02 to 3.31).[25] This finding is interesting, as the patients in the placebo group were likely not harmed by withdrawal effects due to discontinuation of ongoing antidepressant therapy before randomisation as they were in the trials we reviewed.

The clinical benefit of these drugs as assessed on ranking scales like the Hamilton Depression Scale (which is the most commonly used scale to assess benefit for these drugs) is doubtful, as recently confirmed in a large, independent systematic review.[23] Independent reviews are more reliable than those undertaken by the industry, which are four times more likely to show positive effects for their own drug, when compared to independent studies.[26]

We believe that the overall drop-out rate is important, as it reflects the patients' overall assessment of the balance between benefits and harms and whether the patients consider it worthwhile to take the drug.

Our data also showed that patients on SSRIs or SNRIs were two and half times more likely to leave the study due to adverse events (tolerability) compared to patients on placebo. Our estimate (RR 2.63, 2.33 to 2.96) was more pronounced than, and significantly different from, that previously noted for paroxetine, 1.77 (1.44 to 2.18) based mostly on published data,[11] and for all SSRIs taken together, 1.93 (1.23 to 3.03).[24] For the other secondary outcome of drop-outs due to lack of effect, patients on SSRIs or SNRIs were half as likely to leave the study as patients on placebo. However, as noted above, this result is biased and cannot be taken as evidence that the drugs work. When more people drop out because of adverse effects, there will be fewer who can drop out because of lack of effect.

Studying the drop-out rates from RCTs is important to ensure that other recorded outcomes are not biased due to differential drop-out rates and reasons between the treatment arms. [27] Our review underlines that it is important to get outcome data for all randomised patients, not only those who stay on in the trial.

Strengths and limitations of our review

We have undertaken the first meta-analysis of study drop-outs for SSRIs and SNRIs using data from CSRs and were able to demonstrate for the first time that more patients drop out on SSRIs and SNRIs than on placebo. It is possible that a greater difference could have been seen if the included trials did not have serious methodological flaws. As the trials recruited patients already in treatment and had short wash-out periods prior to randomisation, the withdrawal effects could be pronounced[28,29] especially as they may persist many months after people stopped the medication. [21]

The main limitation of our review is that we were unable to include all trials for all commonly used SSRIs and SNRIs, as we were limited by the CSRs made available to us by the regulators. However, as there are only minor differences between the individual drugs within these classes, we feel this is not an important limitation. Another limitation was that our initial plan in the protocol was to have the first data extraction open but to keep the second data extractor blinded. However, due to the format and styling of the CSRs, this was not possible to do. We did a pilot test,[8] and even when the name of the treatment arm was redacted, the text made it clear which arm it was. Lastly, though overall study drop-outs and study drop-outs due to adverse effects have been used widely to measure acceptability and tolerability respectively, they may be considered crude instruments for measuring effectiveness. On the other hand, we find these outcomes highly relevant in trials of antidepressants, as the benefit of these drugs is doubtful, and as they seem to provide a purely symptomatic effect.[21,23,30] Despite these limitations, we feel that our research has important implications for clinical practice.

Conclusion

Our review adds to the growing concern that SSRIs and SNRIs might not have the desired effect and might do more harm than good.[21,23,30, 31] Our review also highlights the importance of using CSRs when undertaking systematic reviews of drugs.

What is already known on this topic
- Clinical study reports (CSRs) provide much more information than journal articles and may reduce bias; they should therefore be used as source documents for systematic reviews of drugs. - Significantly more patients drop out due to adverse events on SSRIs or SNRIs compared to placebo.
What this study adds
- By using CSRs, we were able to demonstrate for the first time that significantly more patients drop out for any reason on SSRIs or SNRIs than on placebo. - By using CSRs, we were able to correct for the fact that some of the patients who dropped out were not counted as drop-outs in the trials.

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Contributors: All authors had complete access to the data in the study. LSG was known by her maiden name Jensen at the time of the study. TS and PCG contributed to the study concept and design, wrote the protocol, and obtained funding. TS, LSG, NF and DMM acquired the data for the study; TS and PCG contributed to the analysis and TS, LSG, NF and PCG contributed to the interpretation of the data. TS developed the first draft of the manuscript and the other authors critically revised it and approved the final version. PCG is the study supervisor and guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: this study is part of a PhD funded by the Laura and John Arnold Foundation for lead author (TS); no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Transparency: The lead author (TS) and study guarantor (PCG) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspect of the study has been omitted. No discrepancies are withheld.

Data sharing: Additional data and the clinical study reports can be obtained from the corresponding author on request.

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Figures

Figure 1: Flow chart of the selection of the relevant studies for inclusion

Figure 2: Overall study drop-out rates on drugs (SSRI or SNRI) versus placebo (acceptability) post-randomisation

Figure 3: Study drop-out rates due to adverse events (tolerability) post-randomisation

Figure 4: Study drop-out rates due to lack of effect post-randomisation

FIGURES

Figure 1: Flow chart of the selection of the relevant studies for inclusion

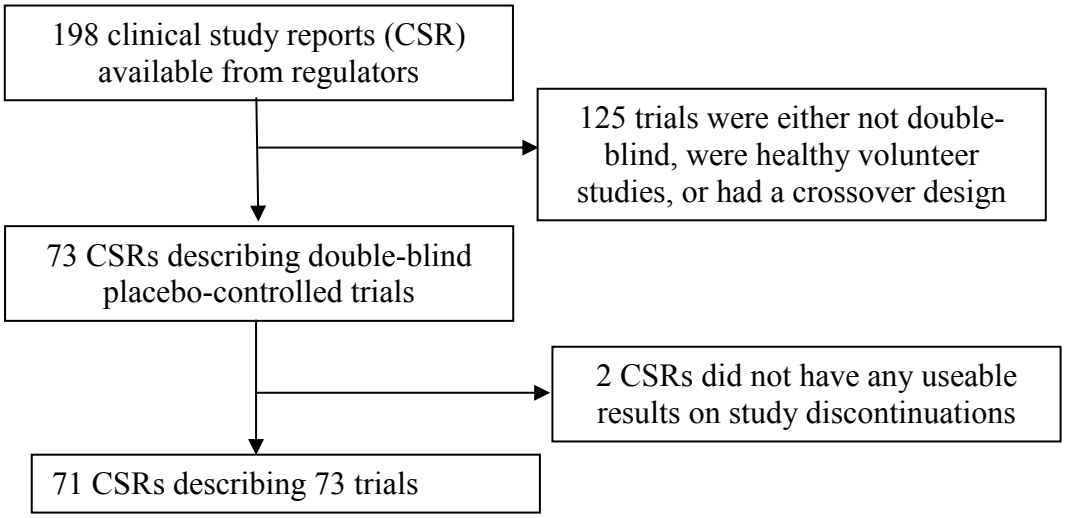


Figure 2a: Overall study drop-out rates on drugs (SSRI or SNRI) versus placebo (acceptability) post-randomisation

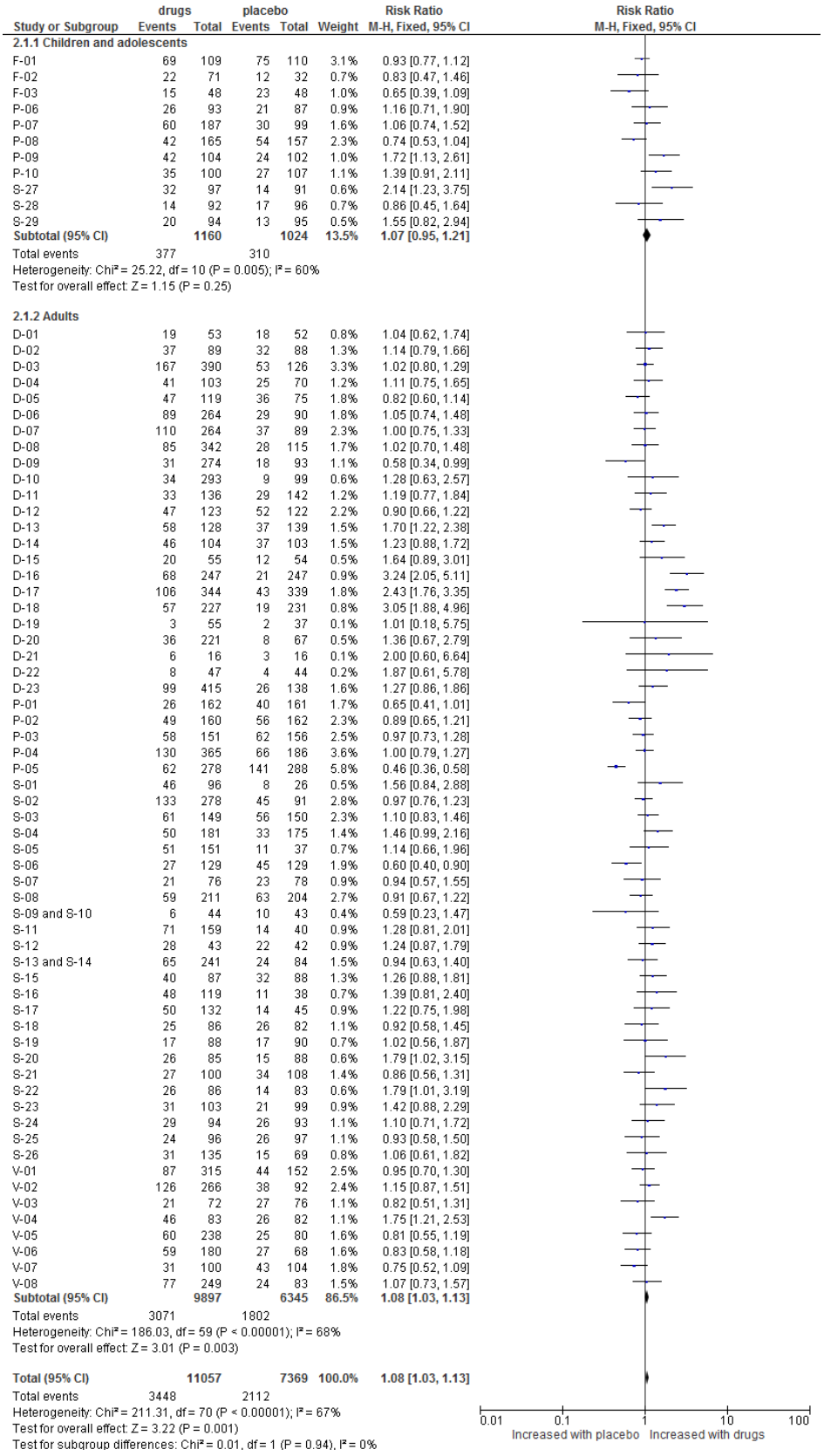


Figure 2b: Sensitivity analyses of overall study drop-out rates on drugs (SSRI or SNRI) versus placebo after exclusion of three trials with a prior single-blind phase of drug

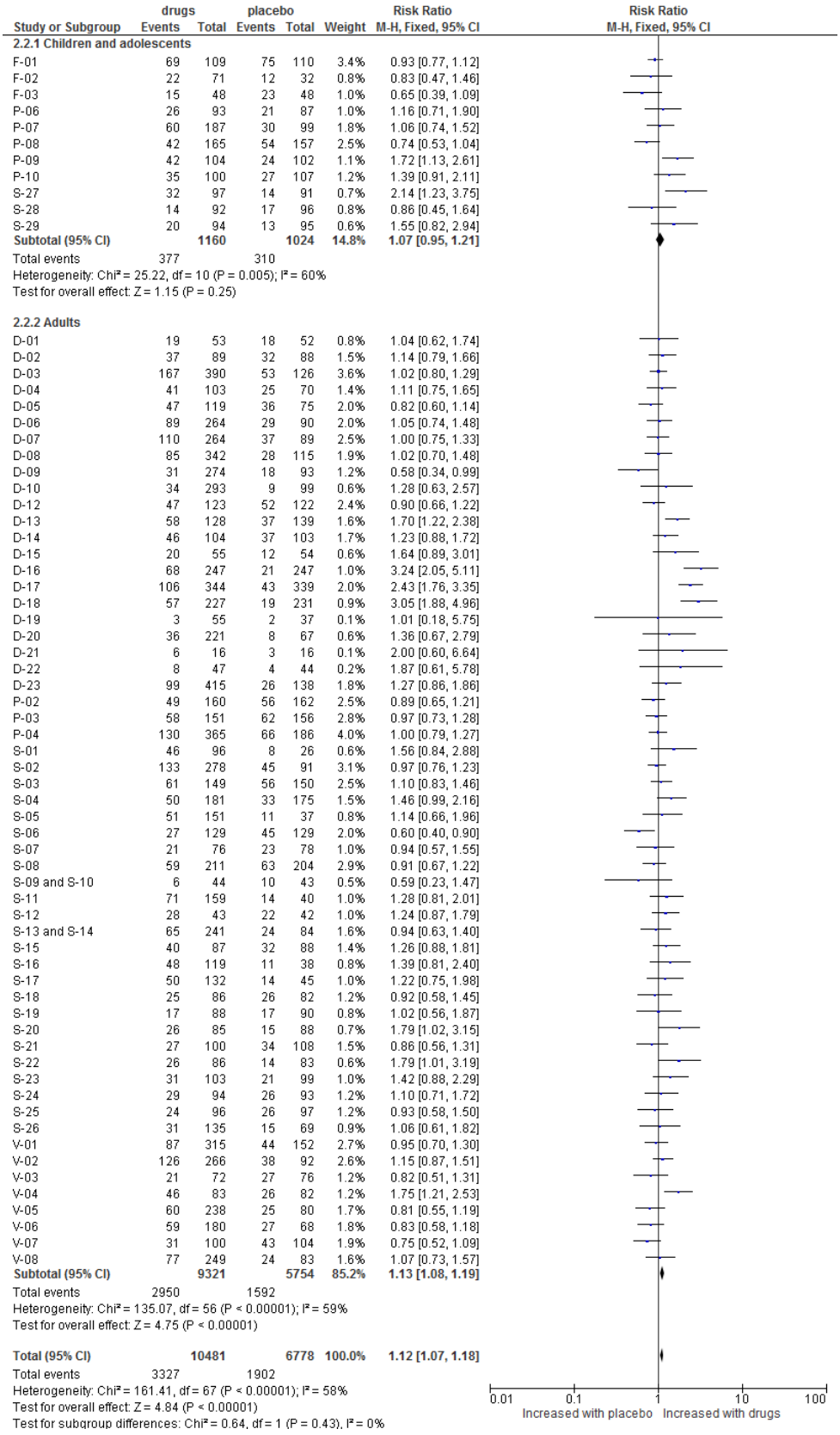


Figure 2c: Sensitivity analyses of overall study drop-out rates on drugs (SSRI or SNRI) versus placebo after exclusion of three trials with fraudulent data or issues with data validity

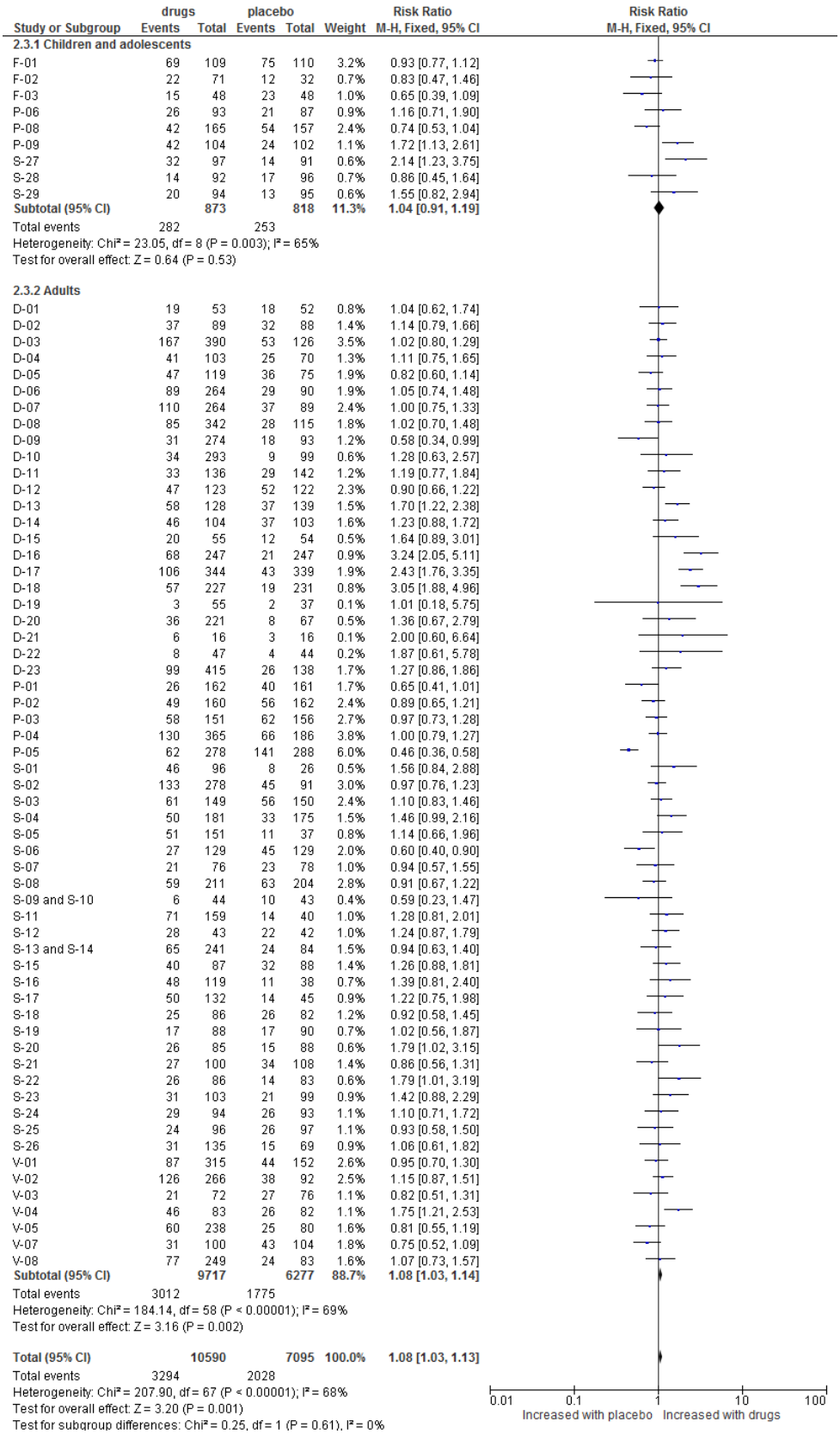


Figure 3a: Study drop-out rates due to adverse events (tolerability) post-randomisation

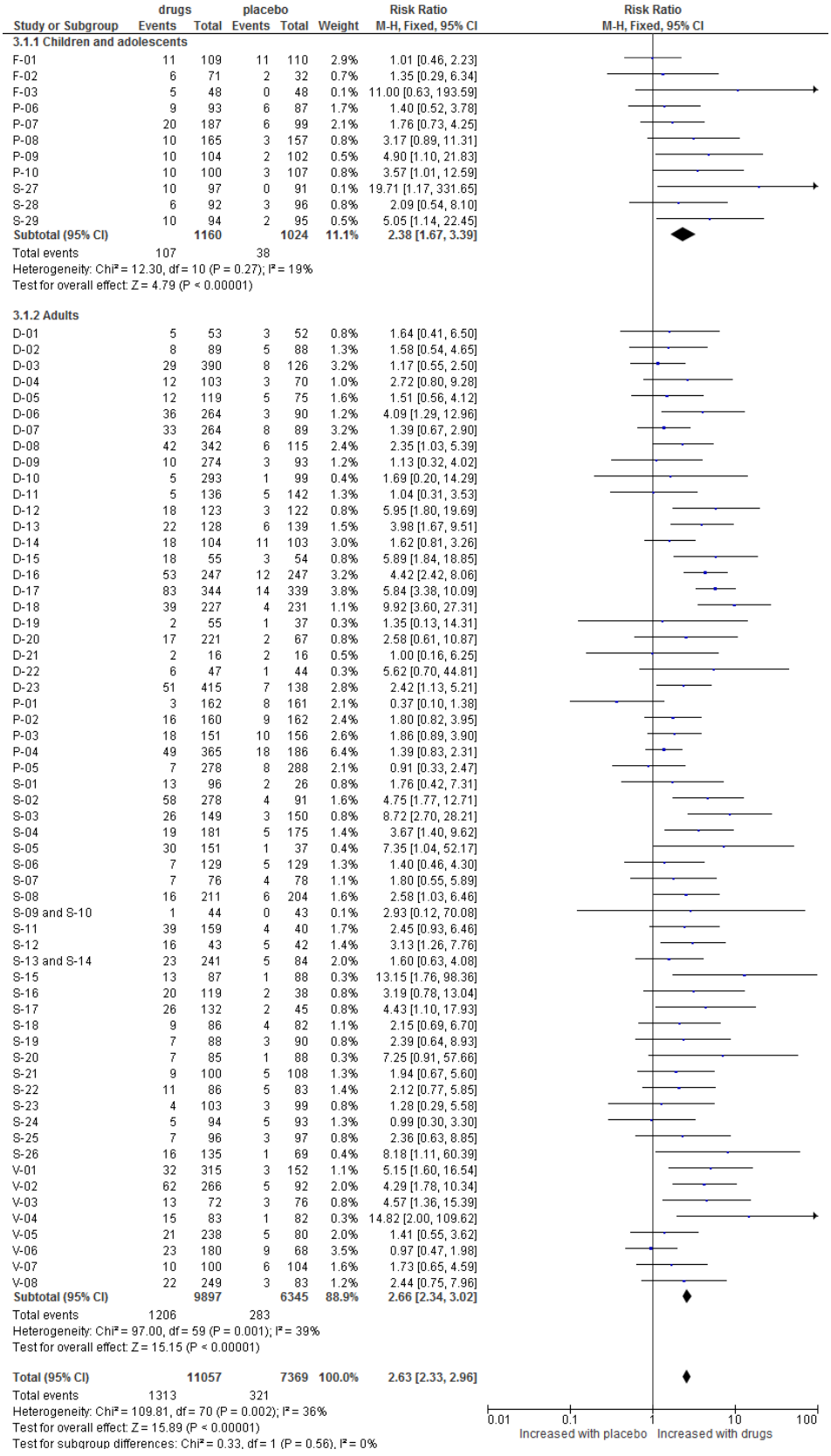


Figure 3b: Sensitivity analysis of study discontinuations due to adverse events using Peto's odds ratio post-randomisation

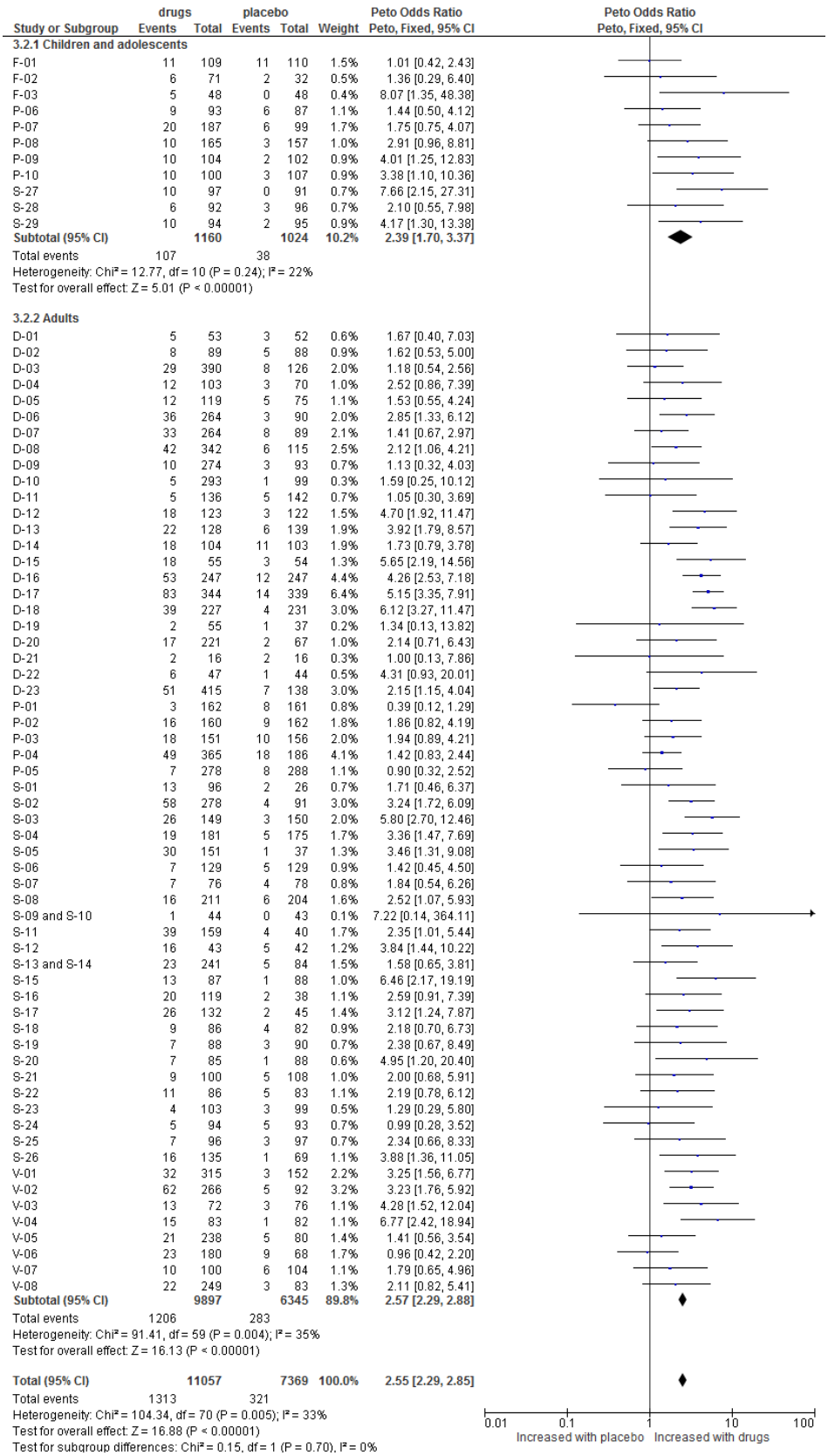


Figure 4a: Study drop-out rates due to lack of effect post-randomisation

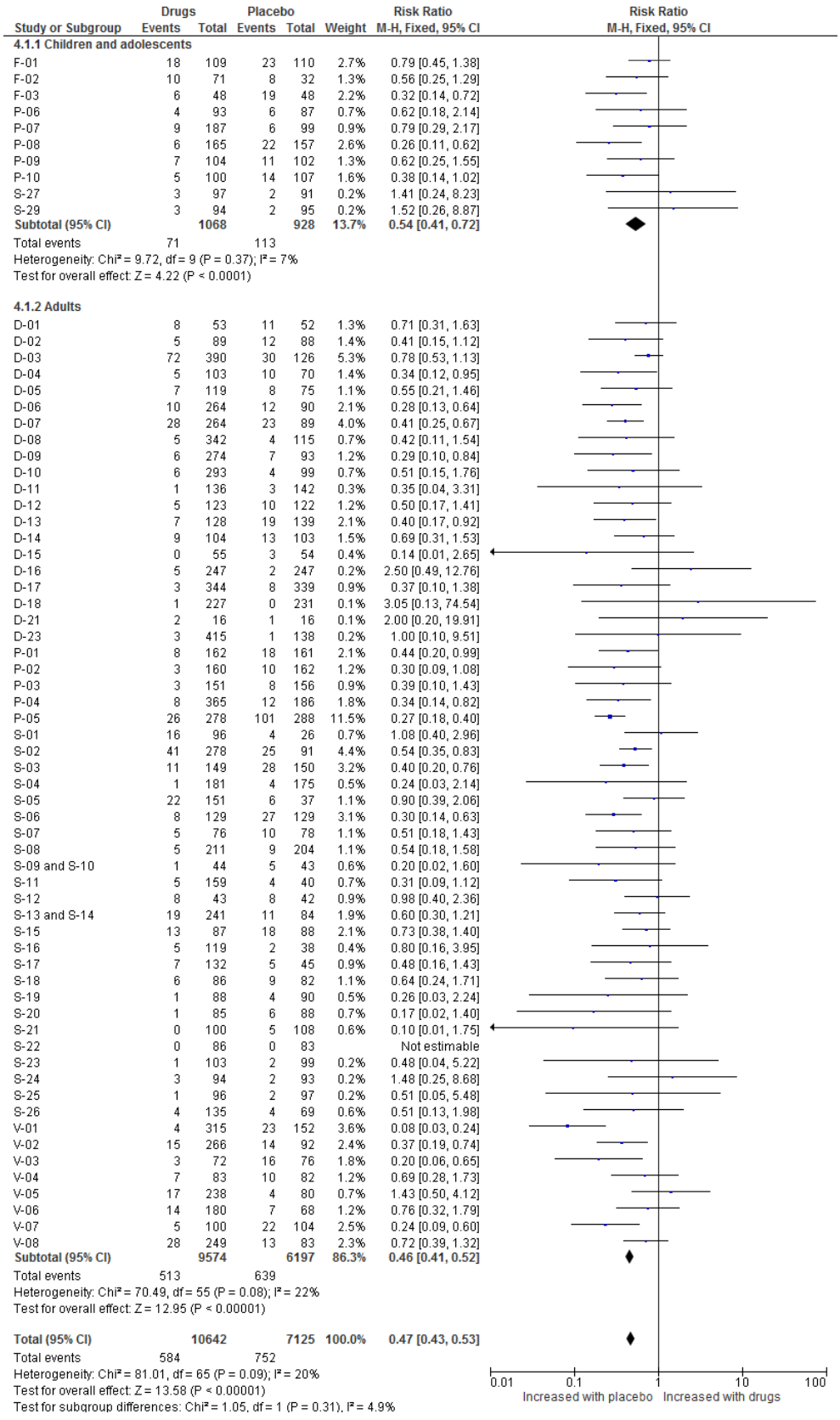
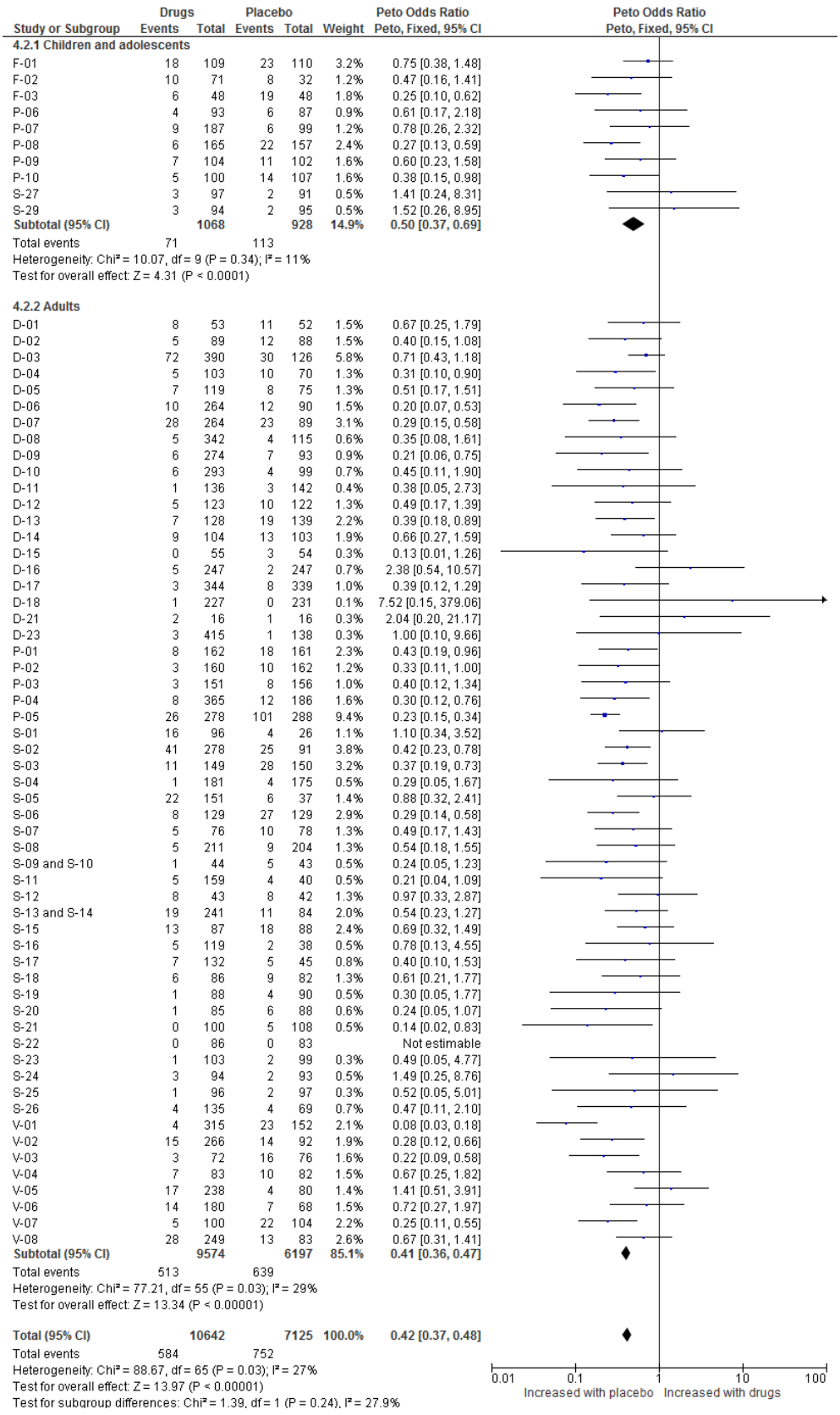


Figure 4b: Sensitivity analysis of study drop-out rates due to lack of effect using Pet's odds ratio post-randomisation



5.4 Research article 4: Selective reporting of quality of life outcomes

Sharma T, Rasmussen K, Paludan-Müller A, Gøtzsche PC. Selective reporting of SF-36 and EQ-5D health related quality of life outcomes in clinical study reports and publications of antidepressant trials *(**draft manuscript**)*.

Selective reporting of SF-36 and EQ-5D health related quality of life outcomes in clinical study reports and publications of antidepressant trials.

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Keywords: quality of life; SF-36; EQ-5D; clinical study reports; antidepressants; publication bias; selective reporting

Abstract: 366 words
Manuscript: 2859 words
Tables: 2
Figures: 2
References: 32
Supplementary Document A – Systematic searches to identify trial publications and their results
Supplementary Document B – Complete results of the comparison of the SF-36 and EQ-5D outcomes in CSRs and publications from companies
Supplementary Document C – Samples of correspondence with the companies

ABSTRACT

Objective: To determine the level of selective reporting and publication bias within clinical study reports and publications for health related quality of life outcomes (HRQoL) in trials of antidepressants.

Design and setting: Structured comparison of clinical study reports, online data and publications of included trials of selective serotonin and serotonin-norepinephrine reuptake inhibitors (SSRIs and SNRIs).

Outcome measures: The HRQoL outcomes of SF-36 and EQ-5D.

Data sources: Clinical study reports (CSRs) of five antidepressant drugs obtained from the European Medicines Agency (EMA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA), corresponding publications identified through systematic searches and obtained from Eli Lilly and Company (Eli Lilly) and Glaxo SmithKline (GSK), and the data available online. Pfizer was also contacted but we did not receive any publications from them.

Data inclusion, extraction and analysis: All double-blind randomised, placebo-controlled trials of SSRIs and SNRIs received from the regulators that included SF-36 and/ or EQ-5D as outcomes in their protocols. The relevant companies Eli Lilly, GSK and Pfizer were contacted for missing data and the publications. The data from the CSRs, that available online and the publications was compared for all outcomes extracted by two researchers independently.

Results: We included 15 trials (19,015 pages of CSRs) on 4717 people though additionally for five trials a HRQoL outcome was used but it was unclear which one and no results were available. This corresponded to six using SF-36, seven using EQ-5D and two using both instruments. There was complete information for SF-36 for only three trials from CSRs and for only two trials from publications out of the eight total and there was complete information for EQ-5D for four trials from CSRs and from none of the publications out of the nine total trials. No complete information was available for SF-36 or for EQ-5D for any of the 15 trials through the data online.

Conclusions: Our review identifies that even CSRs cannot be used as source documents for systematic reviews if HRQoL outcomes are to be considered. Access to full raw data from clinical trials or access to case report forms for all patients would be needed for any comprehensive and reliable review and meta-analysis to be undertaken on this subject.

INTRODUCTION

Much research remains unpublished or is reported selectively,[1-5] which is why calls have been made for using clinical study reports in systematic reviews.[6] Clinical study reports (CSRs) are detailed summaries of trial results prepared by the drug industry for submission to regulatory authorities.[7] Systematic reviews of antidepressants based on CSRs and other regulatory material have shown smaller effects and more harms than when such reviews are based on published articles.[7-10]

Quality of life assessments are particularly selective reported. A review of 101 drug trials found that quality of life outcomes were the least reported patient relevant outcomes, with only 7% having complete information in journal publications.[11] For antidepressants, quality of life assessments have almost universally been left unpublished.[12]

Health related quality of life (HRQoL) scales measure the subjective health and functional status of patients and their general well-being, as seen from their own perspective.[16] The content of these measures can vary from covering generic concepts of functioning (such as physical functioning), through to very disease specific symptoms (such as dexterity for arthritis).[15] The advantages of generic instruments are that they may capture a broad range of aspects of health and the consequences of illness, including harms of treatments, as they focus more on overall well-being and functioning and they can also be used across a wide range of different patient groups.[16]

One of the most widely used generic instruments is the SF-36 (Short-Form-36), which measures health status in eight domains. Physical and mental health component summary scores (PCS and MCS) can be generated from the raw dimension scores.[14-17] Utility measures are generic instruments that estimate the patients' overall preferences to different health states.[13,15] Decision-makers sometimes use them to generate quality-adjusted life years in order to prioritise healthcare resources.[17] The most widely used generic utility measure is the EQ-5D (EuroQol-5D) questionnaire, which contains five dimensions and also has a visual analogue (VAS) scale.[14-15]

Here we describe our systematic comparison of the reporting of HRQoL outcomes of SF-36 and EQ-5D in the CSRs, online data and publications of trials of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs).

METHODS

As reported in our previous study, we requested CSRs for all trials for the commonly prescribed SSRIs and SNRIs for any indication from the European Medicines Agency (EMA) and the UK Medicines and

Healthcare products Regulatory Agency (MHRA).[7,18] We identified those double-blind placebo randomised controlled trials that had SF-36 or EQ-5D as outcomes. The CSRs were converted to a readable format and one researcher (TS) extracted data about study information; the data on outcomes was extracted independently by two researchers (TS and LSG or NF).

Though not initially part of our protocol but based on the findings from our first study,[7] we included results in the companies' online databases; outcomes were extracted by one researcher (TS). One researcher (TS) conducted systematic searches in MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) to identify journal publications of the included trials. The data on HRQoL was extracted by one researcher (TS) (see supplementary document A). However, due to poor indexing it was unclear if all published articles from the trials were identified, or if the publications identified were of the relevant trials as the protocol names were not noted in the publications. Therefore the published articles for the included studies were requested from the three different companies involved (Eli Lilly, Glaxo SmithKline and Pfizer), along with any missing data on SF-36 and EQ-5D results in the CSRs. We also asked for additional information and results for the trials where it was unclear which HRQoL instrument was used. The information about the trials and data on SF-36 and EQ-5D was extracted independently by two researchers (see supplementary document B).

We did not perform any meta-analyses on the results reported in CSRs or publications since there was widespread selective reporting. Furthermore, we had very little data to work and the trials investigated different indications.

Patient involvement

No patients were involved in the design and implementation of the review. We hope to involve patient organisations in the dissemination of our results.

RESULTS

Clinical study reports

We received 198 CSRs and excluded single arm trials (n = 95), healthy volunteer studies (29), one crossover trial, and those trials that did not include SF-36 or EQ-5D outcomes (53) within their protocol, see Figure 1. We excluded an additional five trials (sertraline: protocol 90CE21-0495 and venlafaxine or venlafaxine extended release: protocols 600A-302-US, CA; 600A-313-US; 0600B-209-US, 600A-303-US) that mentioned using a quality of life questionnaire in their protocols but did not state clearly which HRQoL instrument was used. The sertraline trial's protocol mentioned: "*Quality of Life Questionnaire (QoL) - by the patient, total score (maximum 80 points) and Overall Life Satisfaction question (maximum 5 points)",* which

suggests that neither SF-36 nor EQ-5D was used. The abstract stated that: "*There was no significant treatment effect on the change from baseline to endpoint on the Quality of Life scale"* and the results section: "*The change from baseline to endpoint in the Quality of Life Questionnaire also failed to reveal a significant difference between treatment groups*". The CSR noted that the complete results are available in a table 7B, but as EMA only gave us a summary report, we did not have access to any tables. For the four venlafaxine or venlafaxine extended release trials, the CSRs noted: "*Quality of life questionnaires were to be completed by each patient... The questionnaires were developed as a potential tool for assessing the effects of depression and antidepressant medications on patients' perception of the quality of their lives. These included an evaluation of the patient's feelings and mood, satisfaction with life and self, relationship to other people, ability to cope with changes or problems, insight, and control. The questionnaires were not intended to be used as evidence of venlafaxine's efficacy. Therefore, the results from these scales are not included in this report, but they will be the subject of a special report after all the studies have been completed*." We enquired with EMA about these special reports but they did not have them. The details of this missing data are available from supplementary document B.

Thus, we could include 15 trials that amounted to 19,015 pages of CSRs and data on 4717 patients (with 2886 people on SSRIs or SNRIs and 1831 people on placebo) with six using SF-36, seven using EQ-5D and two using both HRQoL instruments, see Figure 1. The study information is summarised in Table 1. Fourteen of the trials were in adults; one paroxetine trial (Protocol 377) was in adolescents and used EQ-5D, which in its original form was not validated for adolescents. The EuroQol group has since 2009 developed a child and adolescent friendly version EQ-5D-Y (which is validated for young people), but this was not available at the time of the trial.[19]

There was considerable selective reporting within the CSRs. Four trials of duloxetine, two of paroxetine and the sertraline trial had incomplete or totally missing HRQoL results. Only three out of eight trials had complete results for SF-36 and four out of nine trials had complete results for EQ-5D. Two trials had no results for SF-36 and one trial had no results data for EQ-5D; additionally there were three trials with partial or unclear data for SF-36 and four trials with partial or unclear data for EQ-5D. For example, for the results of SF-36 in a duloxetine trial, only the physical component score results were labelled; for the rest of the tables, it was unclear what domain they belonged to. More commonly, only one or two of the eight domains of SF-36 had any results, while for EQ-5D, either the utility score or the VAS score was missing (see Figure 2, Table 2 and supplementary document B).

Table 1 Study information on included trials

No.	Trial protocol	Drug	Age (years)	Condition	Dose	Active comparator	SF-36/ EQ-5D
1.	HMAH	duloxetine	18 to 72	MDD	20 or 30 mg per day	None	SF-36
2.	HMAQa	duloxetine	18 to 65	MDD	20 to 60 mg per day	fluoxetine 20mg/ day	SF-36
3.	HMAQb	duloxetine	18 to 65	MDD	20 to 60 mg per day	fluoxetine 20mg/ day	SF-36
4.	HMAW	duloxetine	at least 18	DPNP	60mg BD, 60mg QD and 20mg QD*	None	SF-36 and EQ-5D
5.	HMBOa	duloxetine	at least 18	Fibromyalgia with or without MDD	60 mg per day	None	SF-36
6.	SBAM	duloxetine	18 to 75	SUI in Women electing surgery for severe pure GSI	80 to 120 mg per day	None	EQ-5D
7.	SAAB	duloxetine	18 to 80	SUI or mixed in Women	20mg, 30mg and 40mg per day	None	SF-36
8.	SAAW	duloxetine	18 to 65	SUI in Women	20, 40, or 80 mg per day	None	SF-36
9.	Protocol 595	paroxetine	at least 18	SP	20 to 50 mg per day	None	EQ-5D
10.	Protocol 627	paroxetine	at least 18	PTSD	20 to 50 mg per day	None	EQ-5D
11.	Protocol 648	paroxetine	at least 18	PTSD	20 to 50 mg per day	None	EQ-5D
12.	Protocol 651	paroxetine	at least 18	PTSD	20 or 40 mg per day	None	EQ-5D
13.	Protocol 646	paroxetine	at least 18	GAD	20 to 50 mg per day	None	EQ-5D
14.	Protocol 377	paroxetine	13 to18	MDD	20 to 40 mg per day	None	EQ-5D
15.	STL-NY-94-004	sertraline	18 to 60	SP	50 to 200 mg per day	None	SF-36 and EQ-5D

Data available online

For the trials of duloxetine from Eli Lilly, we could check the online summary reports. None of them had complete information on the outcomes of interest. For one trial (HMBOa), there was no summary report and there was no mention of SF-36 or EQ-5D in three other trials, despite these being secondary outcomes within the study design. Two trials had the component scores results and two other domains (general health and mental health) of SF-36 reported, without any rationale why these were picked out. One of these trials was HMAQa so this allowed us to verify the data from the unlabelled tables in the CSRs for these domains. The Pfizer website on searching stated that trial CSR synopses were only available for trials from 2007 so no information was available online for the one trial of sertraline included. For the paroxetine trials, the

paedactric trial 377 had the complete CSR available online (same as we had received from the regulator) but we were unable to find any relevant data for the remaining five adult trials (see Figure 2, Table 2 and supplementary document B).

Interaction with industry

We contacted the three companies (Eli Lilly, GSK and Pfizer) on 16 April 2016 to request the missing data and trial publications, and we asked Pfizer which HRQoL instrument had been used in its five trials, where this was unclear and also about the results. Only Eli Lilly responded initially (26th April 2016) and sent the publications for five out of their eight trials. We sent a follow-up request (to Eli Lilly about the pending publications and missing data) and they responded (28th April 2016) with the publication for one of the pending trials and the confirmation that the two others remained unpublished but made available links to their online data summaries. They were unable to give us the missing data.

On 17th May 2016, Pfizer responded asking for more information, which we sent a week later, followed by a reminder on 11th July. Pfizer replied on 18th July: *"Pfizer cannot send any study protocols or internal data for the trials requested since this is proprietary information. If you wish Medical Information can conduct a search and send a citation listing with the published studies on "Effects on Quality of Life" for both venlafaxine and sertraline."* On 14th September, we asked for the publications and requested the missing data again reminding Pfizer of the fact that the European Ombudsman ruled in 2010 that there is no commercially confidential information in CSRs and trial protocols. We received a reply from Pfizer a month later where they ignored our request for publications and asked us to fill out Pfizer's online data request form. This was six months after our first letter to Pfizer. The data request form is very detailed and includes a field asking for a date for submission of our results to Pfizer. We felt the demands were inappropriate and considered further interaction with Pfizer meaningless.

After a follow-up email, GSK responded on 13th July by sending a link to their online data and a GSK ID which in combination with the protocol number (29060/protocol number) allowed us to search for the relevant publications. Once again we did not receive any of the missing data. Further details of the data requested and examples of the correspondence with the companies are available in supplementary document C.

Publications

Through our systematic searches, we identified 15 journal publications for 11 of the included trials with no publications for four trials. As their methods were poorly reported, we could not always be totally certain that we had matched the publications correctly to the CSRs (see supplementary document A).

From Eli Lilly, we received 20 journal articles (one was only an abstract with an introduction; it took our library two months to find the full text),[21] but there were no publications for two duloxetine trials (HMAH and SAAB). Using the code GSK had sent us we could find six publications and six conference abstracts from the GSK website. This allowed us to extract data from 33 publications for 13 of the 15 included trials (see supplementary document B). The SF-36 or EQ-5D, or both, were mentioned in only 12 of the 33 publications (36%) and only three of the 12 publications were free of selective reporting (see Figure 2, Table 2 and supplementary document B). For example, for the duloxetine trial HMAW, two publications reported only one of the eight domains of the SF-36 each, the Vitality domain[22] and Bodily Pain domain.[23] In the methods section for the latter it was stated that, "*The change in the Bodily Pain scale from the Medical Outcomes Study Short Form 36 (SF-36 BP) was used as the effectiveness measure*", which was not what was said in the protocol.

For the sertraline trial, where we did not get any publications from Pfizer, the publication we identified through our systematic searches did not have any results for SF-36 or EQ-5D (see supplementary document A).[24]

Table 2 Data availability across the different data sources

Trial	Trial name	Drug	HRQoL type	Data availability		
				Clinical study reports	Online data	Journal article (received from industry)
1.	HMAQa	duloxetine (active comparator fluoxetine)	SF-36	**Partial/ unclear** Results available with tables for component summary scores and individual eight domains, but apart from the physical component score (PCS) results table none are labelled so therefore unclear which results table corresponds to which domain.	**Partial/ unclear** Results available for PCS and MCS component summary scores and domain score results for two of the eight domains (general health and mental health).	**None** No mention of SF-36 in the publication.
2.	HMAQb	duloxetine (active comparator fluoxetine)	SF-36	**Complete** Results available with tables for component summary scores and all individual eight domains.	**Partial/ unclear** Results available for PCS and MCS component summary scores and domain score results for two of the eight domains (general health and mental health).	**None** No mention of SF-36 in the publication.
3.	HMAH	duloxetine	SF-36	**None** The use of SF-36 is stated in the protocol, study design and schedule of events sections; however no results for the instrument are available.	**None** No mention of SF-36 in online summary report.	No journal publications received
4.	SAAW	duloxetine	SF-36	**Partial** Results are available for the individual eight domains. The component summary scores PCS and mental component score (MCS) are unavailable.	**None** SF-36 is stated as one of the outcomes measured in the study design synopsis but results are not given (only results of I-QoL are available).	**None** No mention of SF-36 in any of the publications (only the results for I-QoL).
5.	SAAB	duloxetine	SF-36	**None** The protocol and study design description in main report mentions that HRQoL would be measured by I-QoL and SF-36 but the CSR only has results of I-QoL.	**None** No mention of SF-36 in online summary report (only results of I-QoL are available).	No journal publications received
6.	HMBOa	duloxetine	SF-36	**Complete** Results available with tables for component summary scores for both PCS and MCS and all individual eight domains.	**None** No online summary report available for this trial.	**Complete** Results available for SF-36 from the original publication (and full results for SF-36 also available from the second publication, which has pooled values from two RCTs, HMBOa and another)
7.	HMAW	duloxetine	SF-36 and EQ-5D	**Complete for SF-36 and Partial for EQ-5D** Results available with tables for component summary scores for both PCS and MCS and all individual eight domains for SF-36 and utility scores for EQ-5D (VAS scores are missing)	**None** SF-36 is stated as one of the outcomes measured in the study design synopsis but results are not given.	**Complete for SF-36 and partial EQ-5D** SF-36 fully reported in one publication and selectively reported in 4 publications.. The utility scores for EQ-5D were available (VAS scores are missing).
8.	STL-NY-94-004	sertraline	SF-36 and EQ-5D	**Partial for SF-36 and EQ-5D** Results are available for the individual eight domains for SF-36 and utility scores for EQ-5D. The component summary scores PCS and	**None** CSR Synopses only available for trials from 2007, so no information available for this trial.	No publications received

Trial	Trial name	Drug	HRQoL type	Data availability		
				Clinical study reports	Online data	Journal article (received from industry)
				MCS are unavailable for SF-36 and the VAS scores are missing for the EQ-5D.		
9.	SBAM	duloxetine	EQ-5D	**None** Main report and tables have data for I-QoL and others outcomes but not EQ-5D despite it being stated as an outcome in the protocol/ study design.	**None** No mention of EQ-5D in online summary report (only results of I-QoL are available).	**None** No mention of EQ-5D in the publication, only results of I-QoL available.
10.	Protocol 377	paroxetine	EQ-5D	**Partial** EQ-5D VAS values available but utility results are missing	**Partial** Appendix C online by GSK: so complete data available http://www.gsk.com/en-gb/media/resource-centre/paroxetine/paroxetine-paediatric-and-adolescent-patients/ Same CSR as we have, therefore same results (partial)	**None** No mention of EQ-5D in the publication.
11.	Protocol 595	paroxetine	EQ-5D	**Partial/ unclear** EQ-5D VAS values reported as mean and standard error are needed for comparisons (only median and ranges are reported for double-blind phase), no utility values.	**None** No relevant information available online by GSK	**Partial/ unclear** Only has median change (instead of mean change) for utility values for the intervention arm.
12.	Protocol 648	paroxetine	EQ-5D	**Complete** Data available for EQ-5D VAS and utility	**None** No relevant information available online by GSK	**None** No data on EQ-5D available only results of SDS given.
13.	Protocol 651	paroxetine	EQ-5D	**Complete** Data available for EQ-5D VAS and utility	**None** No relevant information available online by GSK	**None** No data on EQ-5D available only results of SDS given.
14.	Protocol 627	paroxetine	EQ-5D	**Complete** Data available for EQ-5D VAS and utility	**None** No relevant information available online by GSK	**Partial or unclear** Is a pooled study and from the European and South African combined dataset, it states "*paroxetine was significantly superior to placebo in improving quality of life, as rated on the EQ-5D ($p = 0.018$)*"but no further data given.
15.	Protocol 646	paroxetine	EQ-5D	**Complete** Data available for EQ-5D VAS and utility	**None** No relevant information available online by GSK	**None** No data on EQ-5D available only results of SDS given.

DISCUSSION

The lack of publication of HRQoL results from antidepressant trials has been noted previously[11,25] but the extent of selective reporting we found within the CSRs is very disturbing. In many instances, there were no results at all or very limited partial information for the SF-36 or EQ-5D outcomes listed in the protocol in the CSR. We knew that selective reporting may also occur within the CSRs,[7] but the complete absence of results of a secondary outcome within a CSR is alarming. As expected, the lack of data in the companies' online registers and in publications was even worse.

The companies had often included other HRQoL outcomes that were disease specific instruments, such as the Urinary Incontinence Quality of Life Scale (I-QOL) or the functional Sheehan Disability Scale (SDS), alongside the generic SF-36 or EQ-5D instruments, but had then only made the results available for these other instruments. This was also the case when the companies had used their own scales, e.g. the 'Quality of Life in Depression Scale (QLDS)' funded by Eli Lilly[26] or the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) funded by Pfizer.[27] There was not much information in the protocols about the rationale for choosing specific instruments or why the results were reported selectively within the CSRs. Selective reporting has been previously been noted also for the publications of these trials.[25] The primary author for the trial publication that was difficult for us to get access to, [21] was the infamous Dr Charles B. Nemeroff, formerly of Emory University. His serious conflicts of interests and often lack of declaration of all relevant conflicts, kick started ethical discussions in the United States.[28]

There was also very limited data available about the methods used for the analysis of SF-36 and EQ-5D outcomes For example, it was never made clear which country specific value sets were used when EQ-5D utility scores were used in multi-national trials.[29] The method used when data were missing was the 'last observation carried forward (LOCF)', which can produce pretty misleading results,[30-31] and often the initial population that answered the questionnaires was used rather than the IIT population. A review of 352 antidepressant trials noted that only 16% of articles discussed the potential bias associated with the LOCF method, and only 2% calculated the impact of such bias.[32]

Strengths and limitations of the study

The main strength of our study is that it highlights the substantial selective reporting problem of quality of life in antidepressant trials. The many different outcomes and domains gives the sponsor almost unlimited opportunities to pick and choose what to report. Our study was limited by the amount of data that was available to us such that no meta-analysis would have made sense. Moreover, the quality of the data was

very poor and we were also reliant on the response from companies in order to get a complete data set of results, which did not happen as none of the companies gave us any of the missing data we requested.

Conclusions

We have documented that not even the very voluminous CSRs can be trusted when certain outcomes are concerned. The massive amount of selective reporting and the lack of cooperation from the drug companies make us suspect that antidepressants have a negative impact on quality of life.

To get a more reliable view of the benefits and harms of drugs, we will need to have access to anonymised, individual patient data and to a complete set of case report forms. Regulatory agencies should demand complete reporting of all outcomes and should refuse to approve the drugs based on incomplete reporting.

What is already known on this topic
- Clinical study reports (CSRs) provide much more information than journal articles and may reduce bias. - There is significant selective reporting of quality of life outcomes from antidepressant trials.
What this study adds
- We found that CSRs were also completely unreliable for results on HRQoL outcomes and possibly only case report forms or raw clinical trial data would be reliable. - We also found that the online data publically available had the least complete data when compared to CSRs and journal publications for HRQoL outcomes.

Acknowledgments: We thank the European Medicines Agency (EMA) for providing the clinical study reports used for this review. We thank Eli Lilly and Company and GlaxoSmithKline for sending us the publications or for the code to access the publications respectively. We also would like to thank Louise Schow Guski (LSG), Nanna Freund (NF) and Jacob Petersen (JP) for their help with the initial data extraction.

Contributors: All authors had complete access to the data in the study. TS and PCG contributed to the study concept and design, wrote the protocol, and obtained funding. TS, LSG, NF, KR, ASP and JP acquired the data for the study; TS, KR and ASP contributed to the analysis and TS, KR and ASP contributed to the interpretation of the data. TS developed the first draft of the manuscript and the other authors critically revised it and approved the final version. PCG is the study supervisor and guarantor.

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Ethical approval: Not required.

Transparency: The lead author (TS) and study guarantor (PCG) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspect of the study has been omitted. No discrepancies are withheld.

Data sharing: Additional data and the clinical study reports can be obtained from the corresponding author on request.

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Figures

Figure 1: Flow chart of trial selection

Figure 2: Data availability for the outcomes across the different data sources

Figure 1 Flow chart of trial selection

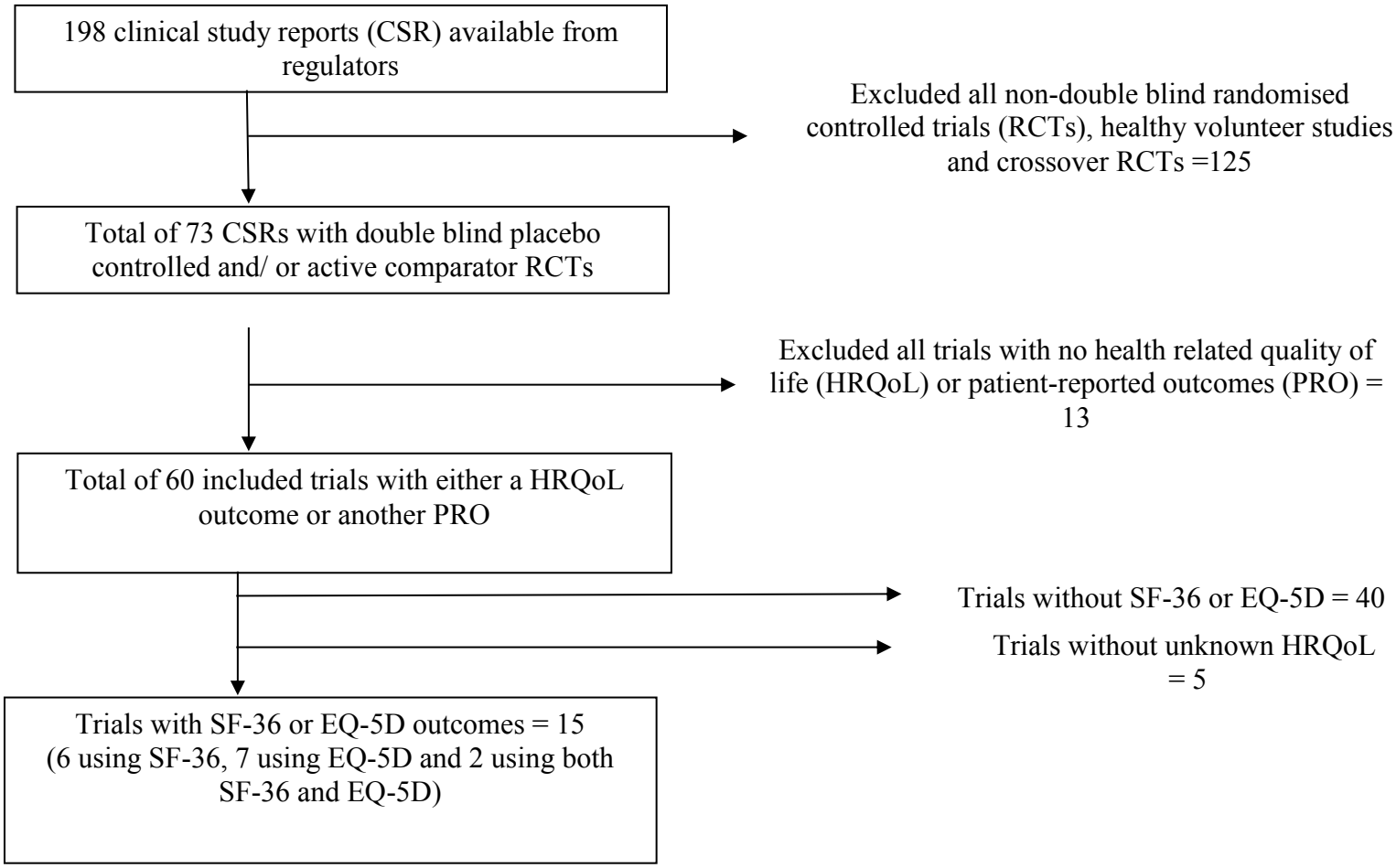
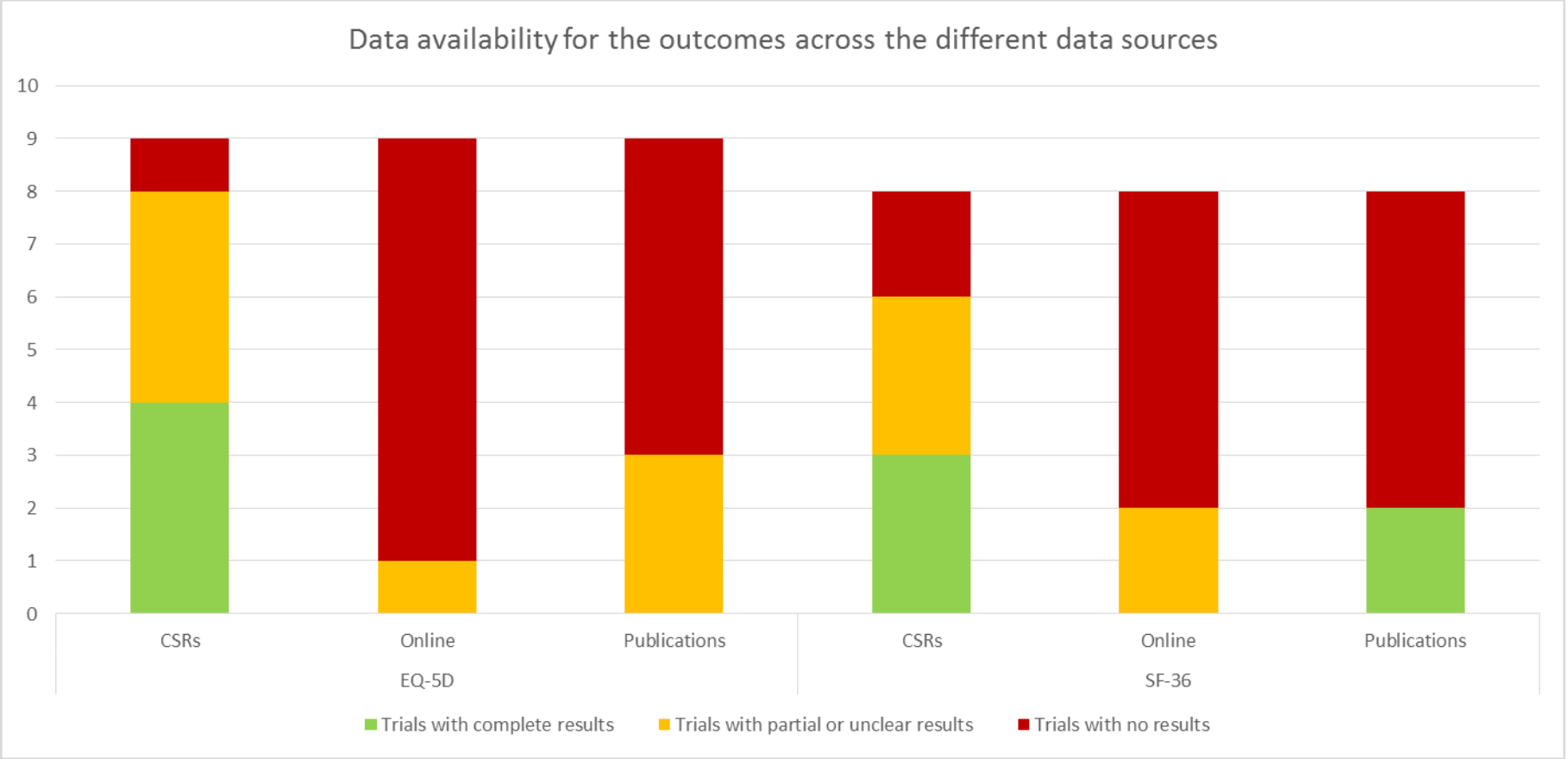


Figure 2: Data availability for the outcomes across the different data sources



6 Appendices

Appendices for research article 1:

Supplementary Data A - Additional details on methods

Supplementary Data B - Included trials characteristics

Supplementary Data C - Case notes on primary outcomes

Supplementary Data D - Additional analyses

Supplementary Data A: Additional details on methods

Table 1: Glossary of terms from clinical study reports[1-3]

Term	Explanation
Clinical study reports (CSRs)	Clinical study reports (CSRs) are detailed summaries of trial results prepared by the drug industry for submissions to regulatory authorities in order to obtain marketing authorization They can be of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.
Adverse events	An adverse event is any undesirable experience associated with the use of a medical product in a patient, which does not necessarily have a causal relationship with this treatment.
Serious adverse event	A serious adverse event as defined by The ICH Guideline on Clinical Safety Data Management, Definitions and Standards for Expedited Reporting is a "any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect."
Adverse event tables	All adverse events occurring after initiation of study treatments are required to be displayed in summary tables. In most cases, it will also be useful to identify in such tables "treatment emergent signs and symptoms" (TESS; those not seen at baseline and those that worsened even if present at baseline). The tables should list each adverse event, the number of patients in each treatment group in whom the event occurred, and the rate of occurrence. Adverse events should be grouped by body system. Each event may then be divided into defined severity categories (e.g., mild, moderate, severe) if these were used. The tables may also divide the adverse events into those considered at least possibly related to drug use and those considered not related, or use some other causality scheme (e.g., unrelated or possibly, probably, or definitely related).
Patient narratives	Patient narratives are brief summaries required by regulatory authorities for certain events such as any deaths, other serious adverse events and other significant events that are of clinical importance (often events that lead to study withdrawal or changes in dose of study medication).
Individual patient listings (IPL)	Individual patient listings (IPL) are lists containing details of events such as patient identifier, the adverse event (preferred term and reported term), duration of the adverse event, severity (for example, mild, moderate, severe), seriousness (serious/non-serious), action taken (none, dose reduced, treatment stopped, etc), and outcome. IPL are also recommended by the authorities for events similar to those for patient narratives, however additionally such lists for all adverse events for all patients are also available (often upon request), and are often placed within appendices.
Appendices	This section is usually at the end of every CSR and should be prefaced by a full list of all appendices available for the study report. The appendices usually should contain the following: protocol and protocol amendments, sample case report form (unique pages only), list of ethics committees, representative written information for patient and sample consent forms, list and description of investigators and other important participants in the study, signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, listing of patients receiving test drug, randomisation scheme and codes, audit certificates (if available), documentation of statistical and

Term	Explanation
	inter-laboratory standardisation methods, publications based on the study and those referenced in the report, patient listings for efficacy outcomes, adverse events (individual patient listings required), discontinuations, protocol deviations, laboratory measurements, other individual patient listings, case report forms (CRFs) for deaths, other serious adverse events and events leading to withdrawals (required) and any other CRFs submitted.
Case report forms (CRFs)	Case report forms (CRFs) are paper or electronic questionnaires specifically used in clinical trial research to collect data from each participating site, by the sponsor of the clinical trial. All the collected data on each patient participating in the trial are therefore contained and/or documented within the CRF, including individual data on adverse events.

Additional information on methods

The clinical study reports (CSRs) were obtained from the regulatory agencies through the freedom of information request route. We requested the European Medicines Agency (EMA) for all their CSRs for all trials they had for paroxetine, fluoxetine, sertraline, citalopram, escitalopram, mirtazapine, venlafaxine, and duloxetine, from their archives. We were then informed that they did not have any documents for fluoxetine and those were available from the UK's Medicines and Healthcare products Regulatory Agency (MHRA), so we requested the CSRs for fluoxetine from them. However, we could not get access to CSRs for all trials for all the commonly prescribed drugs we had requested. We also did not receive any case report forms (CRFs) for any of the trials.

We received in total 198 CSRs but these included a number of open-label studies, healthy volunteer studies and cross-over studies. We only included double-blind placebo controlled trials and then further excluded CSRs of trials where we had no detailed information (patient narratives nor individual patient listings) at all, even for serious events or events leading to discontinuation or change of dose of medication. We excluded these trials as we felt that they would not give us any added benefit of using CSRs, because there would be no additional information regarding our outcomes of interest.

The CSRs were first obtained as scanned PDF documents, but once converted to a readable format using the 'optical character recognition (OCR)' function of Adobe Acrobat XI Professional they could be searched electronically. As a pilot, one report for each drug was randomly chosen and read in its entirety to help understand the different formats of the CSRs and to refine the data extraction form. We had planned that the second observer would extract the data blindly, with the treatment groups masked, but the pilot showed that the format and the language used within the CSRs made blinding impossible.

Search terms

The search terms we used for the primary outcomes of all cause mortality and suicidality were informed by the search strategy developed and used by the FDA[4,5]. The terms for suicidality were quite broad and all search results were verified manually and only confirmed as relevant when the full context and case was read.

For the secondary outcomes the terms for aggressive behaviour were informed by the pilot study and for akathisia we only used the term "akathisia". This was because our pilot showed that unless akathisia was a serious adverse event or one that led to discontinuation, we would not have any patient narrative or the verbatim terms. So if we had only the coded terms (which we expected would be the case for most of the trials), akathisia could be coded as 'hyperkinesia' or other activation terms but not all hyperkinesia events or activation events would necessarily have been akathisia. We felt that we would take the conservative approach and only consider terms where "akathisia" was noted as such. This would of course mean that our

numbers would be under-estimates but we would not have wrongly attributed some events as akathisia, if they were not.

Moreover, the pilot showed that electronically searching alone could not always be trusted (sometimes a space was inserted within a word or an additional letter was registered by the recognition software incorrectly) and relevant synonyms could also be missed. We therefore started with the electronic searches using the defined search terms but then also went through the documents manually to ensure we did not miss any relevant outcomes (except for akathisia as no synonyms were considered) or had picked up irrelevant cases by mistake. It was incredibly laborious but after our pilot we felt this extra step was needed.

Table 2: Terms used for identifying relevant data for the primary and secondary outcomes from CSRs for extraction; the terms were searched through the search function on Adobe Acrobat XI Pro and then any synonyms were identified manually

Primary outcomes	**Search terms**
All cause mortality	death; died
Suicidality	accident; attempt; burn; cut; drown; gas; gun; hang; hung; immolation; injury; jump; monoxide; mutilation; overdose; poison; self damage; self harm; self inflict; self injury; self mutilation; shoot; suicide; suicidal ideation; suicidal thoughts; thoughts of killing one's self; asphyxiation; suffocation; firearm
Secondary outcomes	**Search terms**
Aggressive behaviour	aggression; aggressive behavior; assault; criminal behaviour; damage to property; homicide; homicidal threat; homicidal ideation; hostility; increased anger; increased rage; physical abuse; physically threatening behaviour
Akathisia	akathisia

References:

(1) Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervolgyi V, Kohlepp P et al. Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. PLoS Med 2013; 10(10):e1001526.

(2) Maund E, Tendal B, Hróbjartsson A, Jørgensen KJ, Lundh A, Schroll J et al. Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications. *BMJ* 2014; 348:g3555.

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Supplementary Data B: Trial characteristics of the included 70 RCTs

S. No.	Drug for I	Ind.	Age (years)	Trial	Dose of I mg/day	No. in I arm	Active C	No. in C arm	Dose of C mg/ day	No. in PLB arm	Study R duration (weeks)	Coding dictionary used	Trial phase	Any psycho active or sedative medications permitted	Excluded patients with suicidal risk
1.	duloxetine	MDD	18-65	HMAQa	20 to 60	70	FLX	33	20	70	8	COSTART	2	Y	Y
2.	duloxetine	MDD	18 to 65	HMAQb	20 to 60	82	FLX	37	20	75	8	Not stated	2	Y	Y
3.	duloxetine	MDD	at least 18	HMAYa	40 or 60	188 40: 95 60: 93	PAR	86	20	93	8	Not stated	3	Y	Y
				HMAYa EXT/ CONT*	40 or 60	145 40: 70 60: 75	PAR	70	20	58	26	Not stated	3	Y	Y
4.	duloxetine	MDD	at least 18	HMAYb (Acute)	40 or 60	196 40: 93 60: 103	PAR	97	20	99	8	Not stated	3	Y	Y
				HMAYb EXT/ CONT*	40 or 60	152 40: 71 60: 81	PAR	70	20	71	26	Not stated	3	Y	Y
5.	duloxetine	MDD	at least 18	HMBHa	60	123	None	NA	NA	122	9	Not stated	3	Y	Y
6.	duloxetine	MDD	at least 18	HMBHb	60	128	None	NA	NA	139	9	Not stated	3	Y	Y
7.	duloxetine	MDD	at least 18	HMBC	60	533	None	NA	NA	None	12	MedDRA	3	Y	Y
				HMBC EXT/ CONT*	60	136	None	NA	NA	142	26	MedDRA	3	Y	Y
8.	duloxetine	MDD	at least 18	HMATa	20 or 40	175 20: 91 40: 84	PAR	89	20	90	8	Not stated	3	Y	Y
9.	duloxetine	MDD	at least 18	HMATb	20 or 40	177 20: 86 40: 91	PAR	87	20	89	8	Not stated	3	Y	Y
10.	duloxetine	MDD	18 to 72	HMAH	20 or 30	89	None	NA	NA	88	10	Not stated	2	Y	Y
				HMAH EXT	20 or 30	23	None	NA	NA	23	44	Not stated	2	Y	Y

S. No.	Drug for I	Ind.	Age (years)	Trial	Dose of I mg/day	No. in I arm	Active C	No. in C arm	Dose of C mg/day	No. in PLB arm	Study R duration (weeks)	Coding dictionary used	Trial phase	Any psycho active or sedative medications permitted	Excluded patients with suicidal risk
				/CONT*											
11.	duloxetine	MDD	at least 18	HMAI	5, 10 or 20	390 5: 130 10: 129 20: 131	CLO	132	150	126	8	Not stated	2	Y	Y
				HMAI EXT/ CONT*	5, 10 or 20	185 5: 57 10: 71 20: 57	CLO	64	150	59	44	Not stated	2	Y	Y
12.	duloxetine	MDD with short REM latency	18 to 72	HMAG	20	53	None	NA	NA	52	12	Not stated	2	Y	Y
13.	duloxetine	SUI for Women	at least 18	SBAT	80	247	None	NA	NA	247	12	MedDRA	3	N	N
14.	duloxetine	SUI for Women	18 to 65	SAAW	20, 40, or 80	415 20: 138 40: 137 80: 140	None	NA	NA	138	12	MedDRA	2	N	N
15.	duloxetine	SUI or mixed for Women	18 to 80	SAAB	20, 30, and 40	221 20: 75 30: 69 30/40: 77	None	NA	NA	67	6	Not stated	2	N	N
16.	duloxetine	SUI or mixed for Women	at least 18	SBAX	80	227	None	NA	NA	231	12	MedDRA	3	N	N
17.	duloxetine	SUI or mixed for Women	at least 18	SBAV	80	344	None	NA	NA	339	12	MedDRA	3	N	N
18.	duloxetine	SUI for Women electing surgery for severe pure	≥18 and ≤75	SBAM	80 to 120	55	None	NA	NA	54	8	MedDRA	2	N	N

S. No.	Drug for I	Ind.	Age (years)	Trial	Dose of I mg/day	No. in I arm	Active C	No. in C arm	Dose of C mg/ day	No. in PLB arm	Study R duration (weeks)	Coding dictionary used	Trial phase	Any psycho active or sedative medications permitted	Excluded patients with suicidal risk
		GSI													
19.	duloxetine	SUI, urge, or mixed	30 to 80	SAAA	20	55	None	NA	NA	37	3	Not stated	2	N	N
20.	duloxetine	SUI with Urinary Urgency and PDO	18 to 85	SAAH	30 or 40	16	None	NA	NA	16	1	COSTART	2	N	N
21.	duloxetine	BPH in Men	40 to 85	SAAI	30 or 40	47	None	NA	NA	44	4	COSTART	2	N	N
22.	duloxetine	FM with or without MDD	at least 18	HMBOa	60	104 37 with MDD and 67 with No MDD	None	NA	NA	103 42 MDD and 61 no MDD	12	Not stated	2	Y	Y
23.	duloxetine	DPNP	at least 18	HMAW	60BID[1] 60QD[2] 20QD	342 60[1]: 113 60[2]: 114 20: 115	None	NA	NA	115	12	Not stated	2	Y	N
24.	fluoxetine	MDD	8 to <18 (8 to <13 children 13<18 adolescents)	X065	20**	48	None	NA	NA	48	8	COSTART	3	N	N
25.	fluoxetine	MDD	8 to <18 (8 to <13 children 13<18 adolescents)	HCJE	20 to 60	109	None	NA	NA	110	9	Not stated	3	Y	Y
				HCJE EXT/	20 to 60	FLX/	FLX/ PLB	20	NA	PLB/ PLB	42	Not stated	3	Y	Y

S. No.	Drug for I	Ind.	Age (years)	Trial	Dose of I mg/day	No. in I arm	Active C	No. in C arm	Dose of C mg/ day	No. in PLB arm	Study R duration (weeks)	Coding dictionary used	Trial phase	Any psycho active or sedative medications permitted	Excluded patients with suicidal risk
				CONT*		FLX 20				40					
26.	fluoxetine	OCD	7 to <18 (7 to <13 children 13<18 adolescents)	HCJW	20 to 60	71	None	NA	NA	32	13	COSTART	3	Y	Y
27.	paroxetine	MDD	12 to18 (18+11 months)	329	20 to 40	93	IMI	95	50 to 300	87	8	ADECS	Not stated	N	Y
28.	paroxetine	MDD	13 to 18 (18+11 months)	377	20 to 40	187	None	NA	NA	99	12	ADECS	Not stated	N	Y
29.	paroxetine	MDD	7 to 17	701	10 to 50	104	None	NA	NA	102	8	ADECS	Not stated	N	Y
30.	paroxetine	PTSD	at least 18	627	20 to 50	160	None	NA	NA	162	12	ADECS	Not stated	Y	Y
31.	paroxetine	PTSD	at least 18	648	20 to 50	151	None	NA	NA	156	12	ADECS	Not stated	Y	Y
32.	paroxetine	PTSD	at least 18	651	20 or 40	365 20: 183 40: 182	None	NA	NA	186	12	ADECS	Not stated	Y	Y
33.	paroxetine	SAD/ SP	8 to 17	676	10 to 50	165	None	NA	NA	157	16	ADECS	Not stated	N	Y
34.	paroxetine	OCD	7 to I 7	704	10 to 50	100	None	NA	NA	107	10	ADECS	Not stated	N	Y
35.	sertraline	MDD in hospitals	18 to 65	050-101	50,100, 200 or 400	96 50: 26 100: 24 200: 23 400: 23	None	NA	NA	26	4	Not stated	Not stated	Y	U
36.	sertraline	MDD	18 to 65	050-103	50, 100	278 50: 95	None	NA	NA	91	6	Not stated	2/3	Y	U

S. No.	Drug for I	Ind.	Age (years)	Trial	Dose of I mg/day	No. in I arm	Active C	No. in C arm	Dose of C mg/ day	No. in PLB arm	Study R duration (weeks)	Coding dictionary used	Trial phase	Any psycho active or sedative medications permitted	Excluded patients with suicidal risk
					or 200	100: 92 200: 91									
37.	sertraline	MDD	18 to 65	050-104	50, 100, or 200	149	AMY	149	50, 100, or 150	150	8	Not stated	2/3	Y	N
38.	sertraline	MDD	18 to 65	050-310	50, 100, 200 or 400	151 50: 39 100: 36 200: 38 400: 38	None	NA	NA	37	4	Not stated	Not stated	Y	U
39.	sertraline	MDD or bipolar depression	18 to 70	050-334	50 to 200	129	None	NA	NA	129	6	Not stated	Not stated	N	Y
40.	sertraline	MDD	18 to 60	86CE21-0238	50, 100, 200 or 400	159	None	NA	NA	40	8	Not stated	Not stated	Y	Y
41.	sertraline	MDD	60 and above	86CE21-0247	50 to 200	43	DES	45	25 to150	42	8	Not stated	Not stated	Y	Y
42.	sertraline	MDD	6 to 17	A0501001	25 to 200	97	None	NA	NA	91	10	WHO-ART	3	Y	Y
43.	sertraline	MDD	6 to 17	A0501017	25 to 200	92	None	NA	NA	96	10	WHO-ART	3	Y	Y
44.	sertraline	PTSD	18 or older	93CE21-0640	25 to 200	100	None	NA	NA	108	12	WHO-ART	3	Y	Y
45.	sertraline	PTSD	18 or older	93CE21-0641	25 to 200	86	None	NA	NA	83	12	WHO-ART	3	Y	Y
46.	sertraline	PTSD	at least 18	95CE21-0671	25 to 200	94	None	NA	NA	93	12	WHO-ART	3	Y	Y
47.	sertraline	PTSD	at least 18	96CE21-0682	25 to 200	96	None	NA	NA	97	12	WHO-ART	3	Y	Y

S. No.	Drug for I	Ind.	Age (years)	Trial	Dose of I mg/day	No. in I arm	Active C	No. in C arm	Dose of C mg/ day	No. in PLB arm	Study R duration (weeks)	Coding dictionary used	Trial phase	Any psycho active or sedative medications permitted	Excluded patients with suicidal risk
48.	sertraline	GSP	at least 18	R-0601	25 to 200	211	None	NA	NA	204	12	WHO-ART	3	Y	Y
49.	sertraline	SP	18 to 60	STL-NY-94-004	50 to 200	135	None	NA	NA	69	20	Not stated	3	N	Y
50.	sertraline	OCD	16 to 75	050-336	50 to 200	76	None	NA	NA	78	12	Not stated	Not stated	N	N
51. **52.**	sertraline	OCD	18 or older	86CE21-0237 & 86CE21-248	50 to 200	44	None	NA	NA	43	8	WHO-ART	Not stated	Y	U
53. **54.**	sertraline	OCD	18 or older	88CE21-0371 & 88CE21-0372	50, 100 or 200	241 371:102 372: 139	None	NA	NA	84 371: 38 372: 46	12	WHO-ART	Not stated	Y	U
				88CE21-0371 & 88CE21-0372 EXT/ CONT*	50, 100 or 200	96 371: 40 372: 56 50: 33 100: 25 200: 38	None	NA	NA	22 371: 9 372: 13	48	WHO-ART	Not stated	Y	U
55.	sertraline	OCD	18 or older	91CE21-0546	50 to 200	86	None	NA	NA	82	12	WHO-ART	Not stated	Y	U
56.	sertraline	OCD	6 to 17	90CE21-0498	25, 50 or 200	94	None	NA	NA	95	12	WHO-ART	Not stated	N	N
57.	sertraline	PD	18 or older	90CE21-0514	50, 100 or 200	119	None	NA	NA	38	12	WHO-ART		Y	N
58.	sertraline	PD	18 or older	90CE21-0529	50, 100 or 200	132	None	NA	NA	45	12	WHO-ART	Not stated	Y	N

S. No.	Drug for I	Ind.	Age (years)	Trial	Dose of I mg/day	No. in I arm	Active C	No. in C arm	Dose of C mg/ day	No. in PLB arm	Study R duration (weeks)	Coding dictionary used	Trial phase	Any psycho active or sedative medications permitted	Excluded patients with suicidal risk
59.	sertraline	PD	18 or older	93CE21-0629	25 to 200	85	None	NA	NA	88	10	WHO-ART	Not stated	Y	Y
60.	sertraline	PD	18 or older	93CE2 l-0630	25 to 200	88	None	NA	NA	90	10	WHO-ART	Not stated	Y	Y
61.	sertraline	PD	18 or older	93CE21-0646	25 to 100	103	None	NA	NA	99	10	WHO-ART	Not stated	Y	Y
62.	sertraline	NIDDM	18 to 70	050-113	50 to 200	181	None	NA	NA	175	54	Not stated	Not stated	N	U
63.	venlafaxine	MDD	18 or older	600A-:302-US, CA/302	75 to 200	72	TRA	77	150 to 400 avg.: 294 to 300	76	6	Not stated	3	Y	Y
				600A-:302-US, CA/302 EXT/ CONT*	75 to 200	37	TRA	30	150 to 400 avg.: 294 to 300	29	67.6	Not stated	3	Y	Y
64.	venlafaxine	MDD	18 or legal age of consent or older	0600A1-372-US	200, 300 or 375	157	FLX	158	40, 60 or 80	152	6	COSTART	3	Y	Y
65.	venlafaxine	MDD	18 to 65	0600A-203-US	25, 75, or 125	266 25 mg 89 75 mg 89 125mg 88	None	NA	NA	92	6	Not stated	2	Y	U
66.	venlafaxine	MDD	18 or legal age of consent	600A-303-US	75 to 225	83	IMI	82	75 to 225 avg.: 177	82	6	Not stated	3	Y	Y

S. No.	Drug for I	Ind.	Age (years)	Trial	Dose of I mg/day	No. in I arm	Active C	No. in C arm	Dose of C mg/ day	No. in PLB arm	Study R duration (weeks)	Coding dictionary used	Trial phase	Any psycho active or sedative medications permitted	Excluded patients with suicidal risk
			or older						to185						
				600A-303-US EXT/ CONT*	75 to 225	33	IMI	35	75 to 225	33	51.5	Not stated	3	Y	Y
67.	venlafaxine	MDD	18 to 65	600A-313-US	25, 75 or 200	238 25: 80 75: 76 200: 82	None	NA	NA	80	6	Not stated	3	Y	Y
68.	venlafaxine extended release	MDD	18 or legal age of consent or older	0600B-209-US	75 to 225	100	None	NA	NA	104	8	Not stated	3	Y	Y
69.	venlafaxine extended release	MDD	18 or legal age of consent or older	0600B-367-EU	75 or 150	167 75: 85 150: 82	PAR	82	20	83	8	Not stated	3	Y	Y
70.	venlafaxine extended release	MDD	18 or legal age of consent or older	0600B 1-384-US/EU/ CA	150 to 375	180	IMI	187	50 to 200	68	6	Not stated	3	Y	Y

Y: yes; N: no; U: unclear- no list of inclusion and exclusion criteria only summary information and no access to protocol for confirmation.
I: intervention; C: comparator; PLB: placebo

BID: twice daily; QD: once daily

AMY: amitriptyline; CLO: clomipramine; DES: desipramine; IMI: imipramine; TRA: trazodone; V

BPH: Irritative Symptoms of Benign Prostatic Hyperplasia; diabetic peripheral neuropathic pain; FM: Fibromyalgia; GSI: genuine stress incontinence; GSP: generalized social phobia; MDD: major depressive disorder; NIDDM: patients with non-insulin-dependent diabetes mellitus for obesity; OCD: obsessive compulsive disorder; PD: panic disorder; DPNP: Painful Diabetic Neuropathy; PDO: Proven Detrusor Overactivity; PTSD: posttraumatic stress disorder; REM: short rapid eye movement ; SAD: social anxiety disorder; SP: social phobia; SUI: stress urinary incontinence

ADECS: Adverse Drug Experience; COSTART: Coding System Coding Symbols for a Thesaurus of Adverse Reaction Terms; MedDRA: Medical Dictionary for Regulatory Activities; WHO-ART: World Health Organization Adverse Drug Reaction Terminology

**denotes extension phase or continuation (EXT/ CONT) of trial;*
** notes that patients unable to tolerate fluoxetine could dose every other day instead of daily dosing in trial X065

Supplementary Data C – Case notes for primary outcomes (individual patient numbers removed)

Supplementary data Table 1 All cause mortality (deaths) prior to randomisation: 2 deaths, one on placebo and one on SSRI (duloxetine)

Trial	Start date FPFV	End date LPLV	Condition	Duration of LI period	Drug	Case notes on the death
HMBC	March 2002	July 2003	MDD	12 weeks 533 patients entered an open label single arm LI phase with DLX at v2 for 12 weeks prior randomisation**	DLX open label 60mg/ day	**38Y M patient, at v5 on day 16** Completed suicide by hanging *"..The patient had an 8 year history of suffering from depression without suicidal ideation .....The patient reported the adverse events of night sweats and hot flashes that were still ongoing at the time of death. ...His HAMD item 3 suicide risk score was 1-feeling life is not worth living throughout the trial."*
050-334	Feb. 1992	Feb. 1993	MDD or bipolar depression	4-14 days Single blind PLB LI prior to the 6 weeks of acute phase*	PLB LI	**No patient details available** Death by natural causes "*The investigator was informed by his relatives that death had been ascribed to natural causes and no autopsy had been performed."* No further details available.

FPFV: first patient, first visit; LPLV: last patient last visit; LI: lead-in phase of trial
DLX: duloxetine; PLB: placebo;
Feb.: February; HAMD: Hamilton Rating Scale for Depression; M: male; MDD: major depressive disorder; v: visit number; Y: years
* The study had varying LI phase lengths. 3 patients in SER had no LI phase and went to active treatment at screening. 4 patients in PLB arm had concomitant therapy with antidepressants (TCA or other similar) but whether this patient was on any other medication was not noted.
** There were 533 patients on DLX for 12 weeks open label and this was followed by a total of 278 patients who continued the study and were randomised at v8 to either receive PLB (142) or DLX (136) for a further 26 weeks.

Supplementary data Table 2 All cause mortality (deaths) in acute or randomisation phase: 12 deaths, three on placebo, eight on SSRI and one on imipramine

Trial	Start date FPFV	End date LPLV	Condition	Duration of study phase	Drug	Case notes on the death
HMATa	March 2000	April 2001	MDD	8 weeks This trial had a 1 week PLB LI and a 2 week PLB LO phase after the 8 weeks acute phase.	DLX 40mg/day	**78Y M patient, at v9 on day 60** Cardiac-respiratory arrest resulting in death *"…. Patient's niece notified the site that the patient threw all his study medications away on 8-Sep-00 and no longer wanted to participate in study. The patient refused to return to the site for an early discontinuation visit, and thus was terminated from the study on 11-Sep-00. On 12-Sep-00, the patient's niece went to the patient's home and found him lying on his back and apparently dead.... An autopsy was not performed at the family's request. The death certificate indicated the immediate cause of death as cardio-respiratory arrest.."*
HMAYa	Nov. 2000	July 2002	MDD	26 weeks EXT/ CONT This was the continuation phase (Study Period III) for responders.*	DLX 40mg/day	**44Y F patient, at v14 on day 216** Non-cardiogenic pulmonary oedema resulting in death "*..The patient had a history of hospitalization for worsening of psychotic symptoms in June 2000... On 9 December 2001 the patient had an argument with her husband which made her quite upset, even the following day. During the 9th and 10th of December the patient complained of chest pain (pressure) which a family friend considered a psychiatric symptom. On 11Decemberthe friend attempted to contact the patient but she never answered the phone. The friend then went to the patient's house only to find her lying in bed, barely conscious, no fever, no vomiting. The patient was incontinent of urine in bed ….admitted to taking 5 tablets of oxazepam..."*
HMAYa	Nov. 2000	July 2002	MDD	26 weeks EXT/ CONT This was the continuation phase (Study Period III) for responders.*	DLX 60mg/day	**23Y F patient, at v9 on day 82** Completed suicide by jumping out of a window. **"…."***The patient had been taking cetirizine hydrochloride and budesonide since 1996 for asthma. …on 15-Jan-02, before having breakfast, the patient went to the bathroom and asked her grandma to wait breakfast for her. When breakfast was ready she suddenly went to her room and jumped out the window. The patient gave no warning or explanation for her actions. The patient died. She had been treated*

Trial	Start date FPFV	End date LPLV	Condition	Duration of study phase	Drug	Case notes on the death
						for the past 4 years by the investigator with no previous suicide attempts. The patient was a good student but did have some relationship problems with her mother....."
HMAYa	Nov. 2000	July 2002	MDD	26 weeks EXT/ CONT This was the continuation phase (Study Period III) for responders.*	PLB	**53Y F patient, at v14 on day 222** Completed suicide by hanging. *"..On 30-May-200l the patient began placebo ...on 16 November2001 the patient reported stomach pain so the investigator prescribed omeprazole.....on 21 December 2001 Betacid was prescribed for hypoacidity. On 27 December the patient reported insomnia and began taking zopiclone. The patient again reported insomnia on 3 January 2002 and 5 January 2002 so the investigator suggested that the patient be discontinued from the study. The early termination visit was scheduled for 7 January, but the patient did not attend that visit and on 8 January the patient's husband called to inform the site that the patient hung herself (completed suicide) on 7 January 2002.... The patient had no previous suicide attempt."*
HMAW	June 2001	April 2003	DPNP	12 weeks No LI phase. Patients who completed were reallocated to an extension study**	PLB	**73Y M patient , on day 3** Accidental drowning resulting in death *"..The patient had a history of hypertension and hypertriglyceridemia since 1992, and a stroke that had occurred in June 2001. The patient also had a history of diabetes mellitus since 1995. The patient began placebo on 19 December 2001....On 22 December 2001, 3 days after starting placebo, the patient's wife found him dead in the hot tub. ...No autopsy was performed."*
HMAW	June 2001	April 2003	DPNP	52 weeks EXT/ CONT This was the continuation phase (Study Period III) **	DLX 60mg/ day	**No patient details available** 1 patient had SAE of sepsis and died No further details available.
HMAW	June 2001	April 2003	DPNP	52 weeks EXT/ CONT This was the continuation phase (Study Period III) **	DLX 60mg/ day	**No patient details available** 1 patient had SAE of myocardial infarction and died No further details available.

Trial	Start date FPFV	End date LPLV	Condition	Duration of study phase	Drug	Case notes on the death
SBAX	May 2001	May 2002	SUI for Women	12 weeks The trial had a 2 week PLB LI period and those that completed the study could enter trial SBBM	DLX 80mg/ day	**70Y F patient at v14 on day 222** Multifocal embolic cerebrovascular accident resulting in coma and her eventual death "*...Approximately 5 weeks after receiving study drug, the patient had complaints of painful chest muscles after lifting heavy rocks in her garden. The patient consulted with her physician and was prescribed Diclogenac and Synap Forte. An x-ray was performed and showed two fractured ribs. On 15-Sep-2001, this patient was found in semi-comatose state... experienced a multifocal embolic cerebrovascular accident resulting in coma.... the patient was intubated and a chest x-ray confirmed the presence of rib fractures and showed a left haemothorax. The investigator suggested that the patient may have fallen, which caused the previously fractured ribs to puncture her lung and cause the haemothorax. This required surgical drainage. The haemothorax was thought to complicate her already depressed respiratory function. Benzodiazepine level was higher than normal range, but the patient reported no benzodiazepine concomitant medications.*
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	8 weeks Study had 7 ± 10 days LI and to up to 3 days of taper LO phase followed by 4-10 days of PT.	VEN ER 75 mg/day	**62Y F patient on day 26 (suicide attempt on day 21)** Completed suicide by strangulation (was hospitalised, but ultimately died), noted as post-study event in CSR *"... She was randomly assigned to receive venlafaxine ER 75 mg/day on November 8, 1994. ...Her husband described her as having ´a good day´ on November 27 with nothing to predict her suicidal behavior on the following day. On November 28, she attempted suicide by strangulation (hanging). She was hospitalized and resuscitated before being transferred to an intensive care unit. ..... During the night of December 2 further neurologic deterioration appeared; an angiography showed there was no intracerebral blood flow which was compatible with cerebral death. She died on December 4."*
0600B 1-384-US/ EU/CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The	IMI 125mg/ day	**54Y M patient, on day 25** Completed suicide by hanging. *"On 14 Feb 99, the patient committed suicide by hanging. The patient was brought to the hospital, but died despite attempted resuscitation. He was not reported as having been suicidal before and had shown significant clinical improvement during the study."*

Trial	Start date FPFV	End date LPLV	Condition	Duration of study phase	Drug	Case notes on the death
				LO varied as well***		
050-113	Oct. 1988	Jan. 1992	NID DM	54 weeks Summary report with limited data and no protocol as clinical programme was terminated due to lack of efficacy. The trial noted no LI nor LO study phases****	PLB	**58Y F patient on day 404** Myocardial infarction leading to death. Listed in randomised phase in CSR *"This 58-year-old female, with diabetes mellitus and a history of angina pectoris, received double-blind placebo in this study. Study drug was administered orally from March 30, 1989, to May 6, 1990, a total of 403 days. On May 7, 1990 she suffered an acute myocardial infarction and died."*
648	Feb. 1999	Feb. 2000	PTSD	12 weeks Study had 1 week LI and 2-3 weeks double blind tapering with a 2 week follow up PT	PAR	**38Y M patient, on day 63 and 21 days after last dose** Accidental overdose with ethyl alcohol and PAR noted as post-study event in CSR *"...patient entered R phase on 22-June-1999 & was later terminated from the study due to drinking, protocol violations. Last dose of study medication was reportedly taken on 03-August-1999 and patient's grandmother noted that on 23-Aug-1999, the patient seemed "confused and was hallucinating." On 24-August-1999, approximately 63 days after receiving the first treatment with blinded study medication, and 21 days after receiving the last treatment with blinded study medication, the patient was found dead in his truck with no evidence of external injury or trauma. Toxicology results revealed a high concentration of ethyl alcohol 0.37%. Paroxetine was also detected at 0.58mcg/ml.*

DLX: duloxetine; PLB: placebo; VEN ER: venlafaxine extended release
FPFV: first patient, first visit; LPLV: last patient last visit; LI: lead-in phase of trial; LO: lead-out phase of the trial; EXT/ CONT: extension phase of the trial
DPNP: diabetic peripheral neuropathic pain; F: female; HAMD: Hamilton Rating Scale for Depression; M: male; MDD: major depressive disorder; NIDM: patients with non-insulin-dependent diabetes mellitus, treatment for obesity; Nov.: November; Oct: October; SAE: serious adverse event; Sept.: September; SUI: stress urinary incontinence; v: visit number; Y: years
* The report stated that the "established criteria for entry into Study Period III will be blinded to investigator site staff and subjects." The report states that the criteria were described in the IRB Supplement 1 as part of the appendices. This appendix was however unavailable to us.

**Patients who completed the acute phase of the trial were then randomly reallocated to treatment with DLX 60 mg/day or routine care to further the study for an additional year. We did not have access to the results of this phase; data was only available from the Lilly online summary reports.

* **The results state that PLB LI was for 3-11 days but 1 patient is listed as having only 1 day of LI. The LO planned was tapering of dose for 3 weeks, but only 1 week for Europe, however taper phase could be omitted or adjusted (up to 21 days in US and CA; 10 days in EU) if medically indicated. Data from 4-10 days after therapy was also noted. The death of this patient occurred on day 21 but as the patient was hospitalised.

** **The summary report states "Rationale for Providing a Summary Report: Due to the lack of meaningful long-term effectiveness of sertraline in reducing body weight there will be no further development of this clinical program..... A detailed analysis of the safety of sertraline on all 356 subjects who were enrolled in this clinical trial was reported on 5 April 1994." We did not have access to this detailed analysis. The death occurred on day 404 which is after the 54 week study mark but the narrative suggests that the patient was taking PLB till 1 day prior.

Supplementary data Table 3 All cause mortality (deaths) in lead-out (LO) and/ or post-therapy phases (PT): 2 deaths, one on placebo and one on SSRI (venlaflaxine extended release)

Trial	Start date FPFV	End date LPLV	Condition	Duration of study phase	Drug	Case notes on the death
0600B 1-384-US/EU/CA	Sept. 1997	Nov. 1999	MDD	10-21 days of LO phase.* The trial had a 7 ± 4 days of PLB LI and an acute phase of 6 weeks.	VEN ER 375 mg/ day	**28Y M patient, 3 months after last dose** Cause of death unknown *"...On 20 March 1999, the patient suffered a minor injury. On 8 April 1999, he was hospitalized because of an infection at the injury site. Intravenous antibiotics were given and he subsequently recovered after treatment. Study drug had been discontinued because the patient did not take the medication to the hospital. On 21 July 99, 3 months post study, the patient was found dead. After autopsy, the cause death remained unknown."*
627	July 1998	Jan. 2000	PTSD	Up to 3 weeks of double blind tapering LO phase, followed by 14 days PT (but could range from 2 to 6 weeks PT) ** The trial had a 1 week PLB LI and an acute phase of 12	PLB	**39Y M patient, 17 days after last dose** Completed suicide by shooting *"....The patient received oral study medication (placebo dose level 1) from 13 February 1999. On 19 February 1999, some 7 days after the first dose the patient experienced severe depressive symptoms, which worsened over the next 2-3 weeks. During this time, the patient experienced extreme post-traumatic stress disorder symptoms, including strong feelings of agitation, social withdrawal and* ***suicidal ideation****. ....The patient was diagnosed as having acute depression. The patient was treated for the event with*

Trial	Start date FPFV	End date LPLV	Condition	Duration of study phase	Drug	Case notes on the death
				weeks.		***clotiapine, oxazepam*** *and* ***fluoxetine.*** *Treatment with study medication was stopped due to the depression on 01 March 1999 and the patient was withdrawn from the study. ... On 15 March 1999, the patient underwent electroconvulsive therapy as an out-patient (last treatment of 6) and his condition was reported as much improved. ...On 18 March 1999, some 17 days after the last dose of study medication, the patient committed suicide by shooting himself. "*

PLB: placebo; VEN ER: venlafaxine extended release
FPFV: first patient, first visit; LPLV: last patient last visit; LI: lead-in phase of trial; LO: lead-out phase of the trial;
Jan: January; M: male; MDD: major depressive disorder; Nov.: November; PT: post therapy; PTSD: posttraumatic stress disorder; Sept.: September; v: visit number; Y: years

Supplementary data Table 4 Total number of competed suicides: 6 completed suicides, 1 prior to randomisation, 4 in the acute phase and 1 post therapy (case notes above in mortality tables)

Trial	Start date FPFV	End date LPLV	Condition	LI period	Drug and daily dose	Completed suicides prior to randomisation
HMBC	March 2002	July 2003	MDD	12 weeks	DLX 60mg open label LI	38Y M patient, at v5 on day 16 Completed suicide by hanging

Trial	Start date FPFV	End date LPLV	Condition	R period	Drug and daily dose	Completed suicides in the acute or randomised phase
HMAYa	Nov. 2000	July 2002	MDD	26 weeks EXT/ CONT	DLX 60mg	23Y F patient, at v9 on day 82 Completed suicide by jumping out of a window.
HMAYa	Nov. 2000	July 2002	MDD	26 weeks EXT/ CONT	PLB	53Y F patient, at v14 on day 222 Completed suicide by hanging.
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	8 weeks	VEN ER 75 mg	62Y F patient on day 26 (suicide attempt on day 21) Completed suicide by strangulation (was hospitalised, but ultimately died).
0600B 1-384-US/ EU/CA	Sept. 1997	Nov. 1999	MDD	6 weeks	IMI 125mg	54Y M patient, on day 25 Completed suicide by hanging.

Trial	Start date FPFV	End date LPLV	Condition	Duration of LO/PT phase	Drug and daily dose	Completed suicides in the post therapy phase
627	July 1998	Jan. 2000	PTSD	14 days PT (but could range from 2 to 6 weeks PT)	PLB	39Y M patient, 17 days after last dose Completed suicide by shooting

FPFV: first patient, first visit; LPLV: last patient last visit; LI: lead-in phase of trial; R: randomised or acute phase of trial; LO: lead-out phase of the trial; EXT/ CONT: extension phase of the trial
DLX: duloxetine; IMI: imipramine; PLB: placebo; VEN ER: venlafaxine extended release
Jan: January; F: female; M: male; MDD: major depressive disorder; Nov.: November; Oct.: October; PT: post therapy; PTSD: posttraumatic stress disorder; Sept.: September; v: visit number; Y: years

Supplementary data Table 5 Number of suicide attempts (SA), (including intentional overdoses and intentional self-harm) pre-randomisation: 6 events, 4 on SSRI (duloxetine) and 2 on placebo

Trial	Start date FPFV	End date LPLV	Condition	Duration of LI/ screening	Drug and daily dose	Case notes on the suicide attempts
HMBC	March 2002	July 2003	MDD	12 weeks 533 patients entered an open label single arm LI phase with DLX at v2 for 12 weeks prior randomisation*	DLX 60mg open label LI	**39Y F patient, at v4 on day 11** Intentional overdose on Stilnox *The patient reported two previous episodes of major depression but no history of any previous drug therapy for depression... On 22 September 2002, 11 days after starting study drug, the patient attempted suicide by over dosing on Stilnox 50mg....The patient had no previous history of suicide attempts prior to this event. The patient was discontinued from the study and hospitalized due to patient verbalizing another possible attempt."* The patient had concomitant therapy with zolpidem.
HMBC	March 2002	July 2003	MDD	12 weeks 533 patients entered an open label single arm LI phase with DLX at v2 for 12 weeks prior randomisation*	DLX 60mg open label LI	**30Y F patient, at v7 on day 54** Intentional overdose on DLX, diclofenac sodium and tetrazepam *"The patient started open label duloxetine on 8 October 2002 for Major Depressive Disorder. On 30 November 2002, after an argument with her husband, the patient made a suicide attempt by ingesting all her remaining study medication (about 54 capsules) and 2 capsules of diclofenac sodium (Voltaren) and 2 capsules of tetrazepam (Myolastin).....The patient was hospitalized and treated with gastric lavage and active charcoal. A drug screen was positive for benzodiazapines..... The patient did not experience any events resulting from the overdose... The patient's last dose of study drug was 30 November 2002...discontinued from the study on 3 December 2002."*
HMBC	March 2002	July 2003	MDD	12 weeks 533 patients entered an open label single arm LI phase with DLX at v2 for 12 weeks prior randomisation*	DLX 60mg open label LI	**25Y F patient, at v5 on day 20** Intentional overdose on DLX *"The patient had no previous history of suicide attempt and had one previous episode of major depression ....On 2 October 2002 (visit 4), 9 days prior to event, the patient's HAMD score had dropped to 16 and suicide item# 3 to a score of 0. On 13 October 2002, the patient attempted suicide by ingesting 24 capsules of*

						study drug....The patient immediately reported it to her mother who then took her to the emergency room....The patient had no history of previous suicide attempt noted."
HMBC	March 2002	July 2003	MDD	12 weeks 533 patients entered an open label single arm LI phase with DLX at v2 for 12 weeks prior randomisation*	DLX 60mg open label LI	**No patient details available, at v5** Possible suicide attempt This event was only listed in the appendix within the tables for all adverse events for all patients. The event was "possible suicide attempt" at visit 5, mild for a different patient to the ones listed above during the open single blind DLX phase. No further details are available from the CSR.
377	April 1995	May 1998	MDD paediatric	2 weeks LI. Acute phase was 12 weeks with a 2 weeks LO taper phase of PAR	PLB LI	**17Y F patient, during PLB LI, day unknown** Intentional overdose on bromazepam and valium "*During the screening period the patient experienced moderate emotional lability and tried to overdose on bromazepam.....No other corrective therapy was given....On 24 January 1997, during the placebo run-in and prior to study medication, the patient took an intentional overdose of bromazepam and valium. .... She experienced no side effects as a result of the overdose....the patient had problems at home and had recently had a fight with her boyfriend.*"
377	April 1995	May 1998	MDD paediatric	2 weeks LI. Acute phase was 12 weeks with a 2 weeks LO taper phase of PAR	PLB LI	**15Y F patient, on day 29 (unclear why still on PLB run in)** Slitting of wrist "*On 12 November 1996, the patient started taking 29060 (placebo run-in) for depression. Approximately twenty four days later on 5 December 1996, the patient impulsively slit her wrists following an altercation with her mother. The wounds were superficial and were not stitched. The patient was withdrawn from the study on 10 December 1996, before any active medication was received, because of the poor response by the patient, the parasuicide and the risk of further attempts.*"

DLX: duloxetine; PLB: placebo
FPFV: first patient, first visit; LPLV: last patient last visit; LI: lead-in phase of trial; LO: lead-out phase of the trial;
F: female; M: male; MDD: major depressive disorder; v: visit number; Y: years
* There were 533 patients on DLX for 12 weeks open label and this was followed by a total of 278 patients who continued the study and were randomised at v8 to either receive PLB (142) or DLX (136) for a further 26 weeks.

Supplementary data Table 6 Number of suicide attempts (SA), (including intentional overdoses and intentional self-harm) in the acute phase: 62 events in 59 patients, 40 events in 39 patients on SSRIs, 20 events in 18 patients on placebo and two events in two patients on imipramine

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
HMAI	Dec. 1993	Jan. 1996	MDD	8 weeks Study had 1week (5-7 days) LI and responders entered a EXT/CONT phase	DLX 5mg	**No patient details available, at v5** Suicide attempt This event was only listed in the appendix within the tables for all adverse events for all patients. The event was "suicide attempt" at visit 5, mild for a different patient and not considered a SAE. No further details are available from the CSR.
HMAI	Dec. 1993	Jan. 1996	MDD	8 weeks Study had 1week (5-7 days) LI and responders entered a EXT/CONT phase	DLX 5mg	**No patient details available, at v4** Suicide attempt This event was listed both in the SAE table in the main report, in the appendix within the tables for all adverse events for all patients. The event was "suicide attempt" at visit 4, severe and led to discontinuation. No further details are available from the CSR.
HMAI	Dec. 1993	Jan. 1996	MDD	8 weeks Study had 1week (5-7 days) LI and responders entered a EXT/CONT phase	DLX 20mg	**No patient details available, at v12** Suicide attempt This event was listed both in the SAE table in the main report, in the appendix within the tables for all adverse events for all patients. The event was "suicide attempt" at visit 12, severe and led to discontinuation. No further details are available from the CSR.
HMAI	Dec. 1993	Jan. 1996	MDD	8 weeks Study had 1week (5-7 days) LI and responders entered a EXT/CONT phase	DLX 5mg	**No patient details available, at v4** Intentional overdose This event was listed both in the SAE table in the main report, in the appendix within the tables for all adverse events for all patients. The event was "suicide attempt" at visit 12, severe and led to discontinuation. No further details are available from the CSR.
HMAI	Dec. 1993	Jan. 1996	MDD	8 weeks Study had 1week (5-7 days) LI and responders entered a EXT/CONT phase	DLX 20mg	**No patient details available, at v8 and v9 (2 events)** Intentional overdose This event was listed both in the SAE table in the main report, in the appendix within the tables for all adverse events for all patients. The event was "suicide attempt" at visit 12, severe and led to

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						discontinuation. No further details are available from the CSR.
HMAI	Dec. 1993	Jan. 1996	MDD	8 weeks Study had 1week (5-7 days) LI and responders entered a EXT/CONT phase	PLB	**No patient details available, at v6** Suicide attempt This event was only listed in the appendix within the tables for all adverse events for all patients. The event was "suicide attempt" at visit 6, severe for a PLB patient and considered severe and led to discontinuation. No further details are available from the CSR.
HMAI	Dec. 1993	Jan. 1996	MDD	44 weeks EXT/ CONT This was the continuation phase after the 8 week main randomised phase.	DLX 5mg	**No patient details available, at v17** Suicide attempt This event was listed both in the SAE table in the main report, in the appendix within the tables for all adverse events for all patients. The event was "suicide attempt" at visit 17, severe and led to discontinuation. No further details are available from the CSR.
HMAI	Dec. 1993	Jan. 1996	MDD	44 weeks EXT/ CONT This was the continuation phase after the 8 week main randomised phase.	DLX 10mg	**No patient details available, at v14** Suicide attempt This event was listed both in the SAE table in the main report, in the appendix within the tables for all adverse events for all patients. The event was "suicide attempt" at visit 14, severe but did not led to discontinuation. No further details are available from the CSR.
HMAI	Dec. 1993	Jan. 1996	MDD	44 weeks EXT/ CONT This was the continuation phase after the 8 week main randomised phase.	PLB	**No patient details available, at v16** Intentional injury This event was only listed in the appendix within the tables for all adverse events for all patients. The event was "intentional injury" at visit 16, severe for a PLB patient and considered severe but did not led to discontinuation. No further details are available from the CSR.
X065	April 1991	Feb. 1995	MDD paediatric	8 weeks Study had 1-2 weeks LI and no LO phase	FLX 20mg	**16Y F patient, at v5 on day15** Intentional overdose on tablets of Pamprin, 6 tablets of Momentum, and 15 tablets of Dibromm "*...patient had fight with boyfriend went home and took 8 tablets of Pamprin, 6 tablets of Momentum, and 15 tablets of Dibromm. Patient was taken to emergency room ...by mother.....Patient discontinued from the study. Other AE listed as: manic reaction, insomnia, nausea, nervousness, pallor, and somnolence.*"

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
X065	April 1991	Feb. 1995	MDD paediatric	8 weeks Study had 1-2 weeks LI and no LO phase	FLX 20mg	**17Y F patient, at v4 on day 12** Intentional overdose on unknown pills but possibly Ibuprofen and Phenegran **"...***patient made a suicide attempt and went to the Emergency Room. The suicide attempt was done with unknown pills, possibly Ibuprofen and 4 Phenegran tablets. At the Emergency Room, patient was given activated charcoal with sorbital of 50 gms. Patient was then discharged and sent home. Patient continued in the study and completed the protocol. Other AE listed as: Anxiety, depression, hyperkinesia, migraine, neurosis, thinking abnormal, abdominal pain, asthenia, menstrual disorder, nausea and dysrnenorrhea."*
HCJE	April 1998	July 2000	MDD paediatric	9 weeks Study had 1week PLB LI phase and no LO phase*	FLX Dose unknown	**No patient details available, days on therapy unknown** Intentional Injury (mild) This event was only noted within the adverse events table and no narrative was available
HCJE	April 1998	July 2000	MDD paediatric	9 weeks Study had 1week PLB LI phase and no LO phase*	PLB	**15Y M patient, on day 37** Intentional injury *"...This patient with a prior history of self-mutilatory behaviour was randomized to placebo treatment on 22-December-1998. Patient was hospitalized for suicidal ideation and self-mutilatory behaviour on 28- January-1999. Investigator discontinued patient from study due to this condition. The patient had 37 days of study drug therapy at the time of discontinuation ....Other adverse events included suicidal ideation and homicidal ideation".*
HCJW	March 1999	Aug. 2000	OCD paediatric	13 weeks Study had no PLB LI phase and no LO phase	FLX 20mg	**12YF patient, on day 25/28** Intentional Overdose on acetaminophen *"...The patient received study drug beginning 23-June-1999 and received last dose on 20-July-1999. On 17-Jul-1999, the patient took approximately 20 acetominophen 500mg tablets during a suicide attempt. She experienced nausea and vomiting but did not notify her mother of the overdose until 19-July-1999. Her mother then took her to an urgent care center and labs were drawn. The patient came in for visit 6 on 20- Jul-1999 but neither the mother or the patient told the site about the incident. She was admitted to the hospital on 20-Jul-1999 for elevated liver enzymes. The mother*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						called the investigator on 21-Jul-1999 to report the hospitalization. The patient was discharged from the hospital on 23-Jul-1999..." Two different sections within the CSR noted this incident as occurring on day 25 or on day 28 and the event was noted as "elevated liver enzymes", within the adverse event tables (which was the consequence of the SA).
HCJW	March 1999	Aug. 2000	OCD paediatric	13 weeks Study had no PLB LI phase and no LO phase	FLX Dose unknown	**7Y to 13Y F patient, day unknown** Intentional Injury (moderate) This event was only noted within the adverse events table and no narrative was available and only age group (not actual age) available.
HCJW	March 1999	Aug. 2000	OCD paediatric	13 weeks Study had no PLB LI phase and no LO phase	PLB	**13Y to 18Y F patient, day unknown** Intentional Injury (mild) This event was only noted within the adverse events table and no narrative was available and only age group (not actual age) available.
627	July 1998	Jan. 2000	PTSD	12 weeks Study had a 7 days PLB LI and up to 3 weeks of taper LO phase.	PAR 20mg	**27Y M patient, on day 4** Intentional Overdose on unknown tablets (possibly Lasamet). *"...The patient received oral study medication, paroxetine 20mg, from 02 September 1998. On 05 September 1998, some 4 days after the first dose, the patient was severely depressed and suicidal following a break-up of his relationship, an unwelcome move at work and an argument with his mother, where she accused him of causing a rift in her relationship with his father. At 21:30 hours, the patient took an overdose of unknown tablets (possibly Lasamet). The patient experienced drowsiness for approximately 24 hours following the overdose. The patient did not receive corrective therapy. Treatment with study medication was stopped due to this event and the patient was withdrawn from the study on 05 September 1998....."*
377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PAR 20mg	**18/ 17Y F patient, on day 79/80** Intentional Overdose on PAR **"...**.*On 7 March 1997, the patient received her first treatment with study medication for depression. Approximately eighty days later, on 25 May 1997, the patient attempted suicide using an overdose of*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						study medication. The patient was hospitalised but was given no treatment medication as there were no signs or symptoms associated with the overdose. Study medication was discontinued on 25 May 1997..." The age of this same patient and event was noted as 17 years and 18 years and event date as 79 days and 80 days in two different places in the CSR.
377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PAR 75mg	**17Y F patient, on day 74/75** Intentional Overdose on PAR ***".....**On 7 November 1995, the patient received her first treatment with study medication for depression. Approximately seventy five days later, on 20 January 1996, the patient took an intentional overdose of 28 tablets of study medication. The patient stated that she took the overdose because she felt nervous and was not attempting suicide. ...The patient was hospitalised ....and study medication was discontinued on 20 January 1996. The only sign of the overdose was a mild tremor of the upper extremities..."* The event date is noted as 74 days and 75 days in two different places in the CSR.
377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PAR 30mg	**16Y F patient, on day 69** Intentional Overdose on PAR *"...On 13 November 1997, the patient received her first treatment with study medication for major unipolar depression. Approximately sixty nine days later, on 19 January 1998 at 16:00 hours, the patient took an overdose of six capsules of study medication. The overdose was considered an "impulsive act" and accidental. The patient was not hospitalised and reported no adverse reactions as a result of the overdose. Study medication was not discontinued. The most recent information received on 20 January 1998 reports that the patient has fully recovered. ...other possible etiological factors include the fact that the patient had an argument with her mother."*
377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PAR 20mg	**14Y F patient, on day 53/54** Self-harm and suicide attempt by superficial cuts in the left wrist ***"...**At the time of the event, the patient was suffering from postprandial abdominal pain and headache. On 17 December 1997, the patient received her first treatment with study medication*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						for unipolar major depression. Approximately fifty four days later, on 8 February 1998, the patient attempted suicide after arguing with her mother concerning her decision to marry another man. The patient locked herself in the bathroom and made superficial cuts in her left wrist using a shaving blade. She stated that she did not want to live at the moment, feeling anguish and anger. This episode of crisis lasted approximately two hours, after which the patient calmed and "absorbed" the idea of self destruction. ...Study medication was not interrupted; it was increased. Both the investigator and SB monitor wished for the patient to continue the study under strict supervision....but later was withdrawn due to protocol violation." The incident was noted as 'Emotional Lability/Suicide Attempt' in the narrative and only as emotional lability within the tables and the day of event was listed as 53 or 54 days in different sections of the CSR.
377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PAR 20mg	**15Y F patient, on day 16** Intentional overdose – not stated on what mediction. *".. On day 7 the patient experienced agitation and anxiety lasting 16 days. The investigator considered the experiences to be severe and related to study medication. The patient was on 20mg paroxetine when the adverse experience started. Study drug was stopped on Day 13, and other corrective therapy was given for insomnia, but three days later the patient experienced emotional lability leading to an intentional overdose...."*
377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PLB	**14Y F patient, on day 31** Intentional overdose on clorazepate and PLB *"..On 14 October 1995, the patient received her first treatment with study medication for unipolar major depression. Approximately thirty one days later, on 13 November 1995, the patient attempted suicide by taking an overdose of study medication with Tranxene (clorazepate) [28 x 20mg study medication and 7 capsules clorazepate, dose not specified]. The patient was withdrawn from the study the same day due to protocol violation..."*
377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks	PLB	**15Y F patient, on day 83** Intentional overdose on alprazolam

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
				PLB LI and 2 weeks of taper LO phase.		*"On 29 February 1996, the patient received her first treatment with study medication for unipolar major depression. Approximately eighty three days later on 21 May 1996, the patient took an intentional overdose of the benzodiazipine, Xanax (alprazolam) (21 tablets). The following day she appeared more tired than usual and, after telling her mother what she had done, was taken to hospital. No treatment was required and the patient was discharged the same day.....Study medication was discontinued on 21 May 1996..."*
377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PLB	**17Y F patient, on day 30** Suicide attempt and self-harm by pair of scissors and cigarette lighter. *"....On 6 March 1996, the patient received her first treatment with study medication for depression. Approximately thirty days later, on 4 April 1996, the patient attempted suicide using a pair of scissors, after visiting her mother and being molested by her brother. She stopped when her mother came into the room. The wound was not serious. She has also tried to burn herself with a cigarette lighter. These self-damaging acts were ongoing at the time of reporting. Study medication was discontinued on 1 May 1996. The patient was withdrawn from the study and referred for psychotherapy...."*
701	March 2000	Jan. 2001	MDD paediatric	8 weeks Study had no PLB LI phase and up to 4 weeks of taper LO phase.	PAR 50mg	**16Y F patient, on day 42** Intentional overdose on PAR *"The patient received the first dose of study medication on 05 May 2000. The patient began treatment at a dose of 10 mg/day and was titrated up, in 10 mg/week increments, to the highest dose of 50 mg on 01June2000. On 14-Jun-2000, the patient received the last dose of study medication. She withdrew from the study that day due to lack of efficacy. The patient claimed to have ingested 100 tablets of the taper study medication at 9:30 PM on 15 June 2000, after a fight with her mother. At 4:30 AM the next morning (16 June 2000), the patient informed her mother, who then brought the patient to an emergency room. The patient reportedly felt "shaky" since 1:00 AM. The emergency room doctor stated that the patient "looked okay," but was "slightly tachycardic" with a pulse of 100. The patient was also slightly diaphoretic, with a blood pressure of*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						140/104. ...A urine drug screen was administered, which was found to be negative for approximately 700 compounds including paroxetine and other "antidepressants." The drug screen was positive for caffeine. The patient was referred to an inpatient psychiatric unit...."
701	March 2000	Jan. 2001	MDD paediatric	8 weeks Study had no PLB LI phase and up to 4 weeks of taper LO phase.	PAR 30mg	**11Y M patient, on day 31** Suicide threat with a knife to wrist *"....The patient began receiving treatment with study medication on 10-October-2000. The patient began treatment at a dose of 10 mg/day and was titrated up to the highest dose of 30 mg on 24 October 2000. The patient received the last dose of study medication on 06 November 2000 (Day 28). No reason was given for cessation of medication. On 08-Nov-2000 (Day 30), two days later, the patient held a knife to his wrist and threatened to harm himself. The patient was hospitalized with an acute exacerbation of major depressive disorder. The patient was treated with Wellbutrin® (amfebutamone hydrochloride), and was discharged in stable condition. The event was reported to be resolved on 13-Nov-2000. The patient was withdrawn from the study due to the event...."* This event was listed as 'Acute exacerbation of major depressive disorder [depression aggravated] within the adverse event tables and was only noted as a preparatory SA on reading the patient narrative.
701	March 2000	Jan. 2001	MDD paediatric	8 weeks Study had no PLB LI phase and up to 4 weeks of taper LO phase.	PAR 30mg	**10Y F patient, on day 19** Suicide attempt by smothering with pillows **"....***The patient began treatment at a dose of 10 mg/day and was titrated up, in 10 mg/week increments, to the highest dose of 30 mg on 27 October 2000. The last dose of study medication was taken on 02 November 2000 (Day 20). On 02-Nov-2000 (Day 20), 19 days after the first dose, the patient was hospitalized after a 5-day history of extreme uncontrolled aggression. The patient had been getting "out of control," with acts of aggression and violence. The patient tried to smother herself with pillows in the hospital examination room. The patient was diagnosed with exacerbation of symptoms of major depressive disorder. Treatment with study*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						medication was stopped due to this event, and the patient was withdrawn from the study....”
676	Nov. 1999	Oct. 2001	SAD/SP paediatric	16 weeks Study had no PLB LI phase and up to 4 weeks of taper LO phase.	PAR 20mg	**16Y F patient, on day 38** Self-harm of scratch on right wrist *“...The patient received the first dose of study medication on 17 October 2000 at dose level 1 (10 mg/day), which was increased to dose level 2 (20 mg/day) on 22 November 2000. The last dose of study medication was taken on 28 November 2000 (Day 43). On 21 October 2000 (Day 5), mild lack of emotion was reported. On 23 November 2000 (Day 38), mild emotional lability (self-inflicted scratch on right wrist) was reported. This condition abated in one day without corrective therapy, and was considered to be probably unrelated to treatment with study medication. On 28 November 2000 (Day 43), moderately severe depression (worsening depression) was reported..... and the patient was withdrawn from the study. No taper medication was dispensed, but Paxil® (paroxetine) 20 mg per day was prescribed to treat the worsening depression...”*. The event was noted as ‘Depression (Worsening Depression)’ in the CSR.
329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	PAR 20mg	**14Y F patient, on day 13/14** Intentional overdose on Tylenol *“..On 28-Mar-96, the patient received her first dose of study medication. On 10-April-96, the patient had overdosed on Tylenol. She had ingested 27 or 28 capsules in response to being grounded and was taken into an emergency room for her stomach to be pumped. She was released and scheduled for follow-up liver function test. On 14-April-96, the patient was withdrawn from the study....”* The CSR noted the event as Emotional lability (Tylenol overdose intentional/asymptomatic) in the narrative and as emotional lability in the adverse event tables. Date of event was noted as day 13 in one place and day 14 in another in the CSR.
329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	PAR 40mg	**15Y F patient, on day 37** Intentional overdose on PAR *“....On 14-Mar-96, the patient received her first dose of study medication. The patient exceeded compliance from 19-April-96 through 09-May-96. The overdose was rated by the investigator as*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						serious, moderate in intensity ...the patient continued in the study and completed the acute phase ...on 09-May-96...”
329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	PAR 20mg	**18Y M patient, on day 12** Self-harm with superficial cuts and suicide attempt planned by jumping off the roof *On l 7-May-96, the patient received his first dose of study medication. On 28-May-96, the patient was hospitalized for psychosis with auditory hallucinations and superficial cuts. A voice commanded him to hurt himself. All the cuts closed without medical attention. The voice also commanded the patient to jump from the roof. Although the patient went to the roof he did not jump. It was determined that the patient was a risk to himself. Study medication was discontinued on admission. ....”*
329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	PAR 20mg	**15Y F patient, on day 57** Intentional overdose on PAR and multiple other drugs (Advil, Ibuprofen, Tylenol, fiorinal and unknown white pills) *“... On 15-Feb-95, the patient received her first dose of study medication. She completed the week 7 visit of the acute phase on 05-Apr-97. Following a disagreement with her mother, on 12-Apr-95, the patient intentionally overdosed. She consumed 12 tablets of study drug (level 4), 23 Advil, 12 Ibuprofen 400's, 23 Ibuprofen 600's, 29 "long skinny white pills", 4 Tylenol's and 10 fiorinal tablets. The patient reported headache, constipation, myalgia, myasthenia, and dizziness. The patient was withdrawn from the study on 12-Apr- 95, prior to completion of the final study visit....”*
329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	IMI 200mg	**13Y F patient, on day 31** Self-mutilation *“...The patient received her first dose and last dose of study medication on the 30-August-1996 and 12-0ctober-1996, respectively. On the 29-Septermber-1996, the patient experienced depression and self mutilation for which she was hospitalized. ..In the evening of the Ol-October-96, the patient started down level titration at level 3. Then on the 12-0ctober-96, she decided to stop taking study medication and she eventually withdrew from the study on the 16-0ctober-96....”*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
93ce21 -0640	May 1994	March 1996	PTSD	12 weeks Study had 1week PLB LI phase and no LO phase	SER 25mg/day	**39Y F patient on day 4** Intentional Overdose on SER *"The patient had a history of physical and sexual assault and grew increasingly symptomatic after an encounter with a previous assailant. She had been on 25 mg sertraline daily from 10/24 - 10/26/95, and on 10/27/97 ingested 425 mg sertraline (17 tablets) in an effort to obtain symptomatic relief. She suffered no sequelae of the overdose, and returned to the study site for her visit on 10/31/96 at which time it was determined that she had decompensated, and she was discontinued from the study ..."*
93ce21 -0640	May 1994	March 1996	PTSD	12 weeks Study had 1week PLB LI phase and no LO phase	PLB	**33Y F patient, on day 10** Self-harmful behaviour (mild aggressive reaction) *"Mild aggressive reaction (self-harmful behaviour), depersonalization, and emotional lability of 1-2 days duration, all resolving by the day of the last dose. Investigator felt latter two were pre-existing Axis II traits not noted at screening. Patient claimed history of self-harmful behaviour, not reported at screening."* Patient was discontinued from the study and moderate anxiety was also noted.
86CE2 1-0238	May 1987	May 1989	MDD	8 weeks Study had 1week PLB LI phase and 2 weeks (week 9 and 10) of taper LO.	SER 50mg	**33Y F patient, on day 7** Intentional Overdose on SER *"Patient ...was discontinued after 7 days of double-blind therapy as the result of a suicide attempt in which she ingested 27 capsules of study medication (3 capsules of sertraline 50 mg[=150 mg total and 24 capsules of placebo). The patient was not hospitalized, but reported headache and diarrhoea tor 2 days subsequent to the event..."*
86CE2 1-0238	May 1987	May 1989	MDD	8 weeks Study had 1week PLB LI phase and 2 weeks (week 9 and 10) of taper LO.	PLB	**29/30Y F patient, on day 49** Intentional Overdose on chloral hydrate and beer *"Patient ...was discontinued after 55 days of double-blind medication after ingestion of 5 quarts of beer and 15,000 mg of chloral hydrate in a suicide attempt. The patient was hospitalized and received treatment...."* The event was coded as a suicide attempt occurred on day 4. The patient's was listed as 29 and as 30 years in two different tables.

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
A0501 001	Dec. 1999	May 2001	MDD paediatric	10 weeks Study had no PLB LI phase and no LO phase	SER 100mg	**10Y F patient, on days 35-49** Suicidal treat with a kitchen knife to the neck *"The subject developed increasing suicidal ideation with a plan, beginning on 12 March 2001, 35 days after beginning sertraline. The subject was treated with sertraline 25 mg/day from 06-08 February 2001, 50 mg/day from 09 - 27 February 2001, and was taking 100 mg/day of sertraline from 28 February 2001 up to the onset of the event. Reportedly, the subject held a kitchen knife to her neck while alone but did not cut herself. She was scheduled for a study visit on 19 March 2001 and reported the suicidality, at which point she was hospitalized and discontinued permanently from the study. ..."* The event was noted as suicidal ideation with a plan.
A0501 017	Feb. 2000	March 2001	MDD paediatric	10 weeks Study had no PLB LI phase and no LO phase	SER 150mg	**16Y F patient, on day 48/50** Intentional Overdose on multiple drugs **"...***the subject attempted suicide by multi-drug overdose. The subject was involved in a family argument regarding school attendance.....She was hospitalized and study drug was permanently discontinued. The subject ingested unknown quantities of ibuprofen, Naprozen, aspirin, acetaminophen/pseudoephedrine, brompheniramine/pseudoephedrine, and dimenhydrinate...."* The event was coded as a severe suicide attempt and noted as occurring on 48 days of therapy in one table (discontinuations), and on day 50 in the SAE table for the same event and patient.
A0501 017	Feb. 2000	March 2001	MDD paediatric	10 weeks Study had no PLB LI phase and no LO phase	SER 100mg	**6Y M patient, on day 34** Suicide attempt by threatening to jump out of a moving vehicle *"Sertraline was administered orally from 08 October 2000 until 10 November 2000, a total of 34 days. Total daily dose at onset of event was 100 mg. On 10 November 2000, the subject attempted suicide by threatening to jump from a moving vehicle stating that he wanted to kill himself. Later that same evening he expressed suicidal ideation and was hospitalized. Events that may have affected the subject were: 1) his grandmother attempted suicide 2 weeks earlier and 2) his mother informed him that he was going to be withdrawn from the study and that he was to start psychotherapy..."*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
A0501 017	Feb. 2000	March 2001	MDD paediatric	10 weeks Study had no PLB LI phase and no LO phase	PLB	**17 Y F patient, on day 14** Suicide attempt by immolation *"Placebo was administered orally from 18 January 2001 to 31 January 2001. On 26 January 2001, on the ninth day of study drug, the subject attempted suicide by immolation. Her siblings doused the flames immediately. She was left with minor burns on her abdomen and one on her left shoulder that were treated with topical antibiotics. The subject admitted that she was angry with her parents for going away and leaving her alone at home, because she was fearful. The subject admitted that she had acted impulsively and had not intended to kill herself. The subject's parents did not report this event until 01 February 2001 because they felt the subject's burns were small and she was recovering. Placebo was permanently discontinued on 01 February 2001 due to insufficient clinical response, and she was started on sertraline (50 mg/day). The subject was administered chlorpromazine for sedation. There was no evidence of psychosis or clear premeditation leading to the event..."*
A0501 017	Feb. 2000	March 2001	MDD paediatric	10 weeks Study had no PLB LI phase and no LO phase	PLB	**16Y F patient, on 62 days and 66 days (2 events)** Suicide attempt by hanging and then overdose attempt with PLB One event noted as post study event in CSR *"Placebo was administered orally from 21 November 2000 to 25 January 2001, a total of 66 days. On the subject's last study visit (end of week 10), the investigator was informed that the subject had attempted suicide twice: on 22 January 2001, after an argument with her brother, she tried to hang herself and was prevented from doing so by her family. Three days later, on 25 January 2001 she consumed 32 tablets of study drug. She suffered no side effects following consumption of placebo tablets but was hospitalized for suicidal ideation and further management. The suicidal ideation resolved on 03 February 2001, but the subject continued to remain in the hospital for social reasons. The subject was considered to have completed study treatment and the event was coded in AEM as a post-therapy event. The subject had no relevant history or other illnesses present at the onset of the event. No known concomitant therapy was taken..."*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
88CE21-0371 & 88CE21-0372	Dates unknown	Dates unknown	OCD	12 weeks Study had 1 week PLB LI phase and completers continued in a EXT/CONT phase	SER 200mg/day	**No patient details available, days on therapy unknown** Suicide attempts (1 severe) This event was only noted within the adverse events table and no narrative or further was available.
88CE21-0371 & 88CE21-0372	Dates unknown	Dates unknown	OCD	48 weeks This was the EXT/ CONT part of the study and had a 4 weeks of taper LO phase	SER 200mg/day	**No patient details available, days on therapy unknown** Suicide attempts (1 moderate) This event was only noted within the adverse events table and no narrative or further was available.
050-310	Dates redacted	maybe May 1988	MDD	4 weeks Study had 7-14 days PLB LI phase and no LO phase	SER 100mg	**No patient details available, days on therapy unknown** Suicide attempt *"One patient ...sertraline 100mg), received one capsule of amitriptyline following a suicide attempt on of the double-blind treatment period. Thereafter, the patient returned to double-blind medication as scheduled. No data have been excluded from any analyses as a result of this occurrence."* The event was only obtained in the section related to the deviations from the protocol (due to the use of AMY an excluded medication). The CSR had a table in the appendix on 'Incidence or side effects (all causalities)', but no suicide attempt was listed there and unclear what it was coded as.
050-310	Dates redacted	maybe May 1988	MDD	4 weeks Study had 7-14 days PLB LI phase and no LO phase	SER 200mg	**No patient details available, days on therapy unknown** Suicide attempt The table listing the reasons for discontinuation have noted 1 suicide attempt for 200mg that led to discontinuation, but no narrative is available for us. The following section which may have relevant details have been redacted (blackened) and the subsequent pages "*removed due to confidential patient information*".
050-310	Dates redacted	maybe May 1988	MDD	4 weeks Study had 7-14 days PLB LI phase and no LO phase	PLB	**No patient details available, days on therapy unknown** Suicide attempt by intoxification **(2 events noted)** The table listing the reasons for discontinuation and main report text reporting on discontinuations state that

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						"...patient in the placebo group, a (redacted text) year old discontinued after (redacted text) of treatment having had inadequate response and making two suicidal at tempts ("intoxication" on both occasions)."
050-334	Feb. 1992	Feb. 1993	MDD or bipolar depresson	6 weeks The trial had a 4 to 14 days of PLB LI and no LO phase***	PLB	**41 Y F patient, on day 12** Intentional overdose on centrally acting drugs *"....She had suffered 5 episodes of depression over the previous 11 years but had never attempted suicide before. She was receiving prazepam until her suicide attempt on Day 12 and had been treated with clomipramine until one week before the study...."*
050-334	Feb. 1992	Feb. 1993	MDD or bipolar depresson	6 weeks The trial had a 4 to 14 days of PLB LI and no LO phase***	PLB	**37Y F patient, on day 37** Suicide attempt, no further details ***"....****a 37 year old female was classed as markedly ill on entering the study after 3 weeks of depression.... She had not been given antidepressants during this episode but had been taking* ***diazepam*** *until 8 days before her suicide attempt on Day 37, when it was replaced with a combination of aceprometazine/ meprobamate. She had suffered 10 episodes of depression over the previous 24 years and had attempted suicide on 5 occasions."*
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	8 weeks Study had a 7 ± 10 days PLB LI and up to 3 days of taper LO phase.	PAR 20mg	**64Y M patient, on day 43** Intentional Overdose on paracetamol and vodka *"..The current episode of depression started in July 1994 when his wife died. He had taken an overdose of meptaxinol (4 tablets of 200 mg) on November 3, 1994. He was randomly assigned to receive paroxetine on November 22, 1994. ...and the patient was not suicidal. ...Over the Christmas holidays, he began to miss his wife and started to drink. On January 3, he drank 2/3 of a bottle of vodka and ingested approximately 50 tablets of paracetamol (500 mg). He was hospitalized and ...was discharged on January 5, 1995 with a treatment of Seroxat 20 mg..."*
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	8 weeks Study had a 7 ± 10 days PLB LI and up to 3 days of taper LO phase.	PAR 20mg	**37Y M patient, on 38** Intentional Overdose on sulphasalazine, propranolol and zolpidem (doses unknown) and alcohol. *"...He had a childhood history of behavioral problems, including rages, and had taken an overdose in 1982. The present episode of*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						depression was considered to be his first and had started in June 1994. He was randomly assigned to receive paroxetine on December 22, 1994. There is some doubt whether he took study medication from January 7 until January 28. On January 28, the patient was hospitalized for an overdose with sulphasalazine, propranolol and zolpidem (doses unknown) and alcohol. No study medication was taken in the overdose. The patient was discharged from hospital on January 29 after the treatment code was broken..."
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	8 weeks Study had a 7 ± 10 days PLB LI and up to 3 days of taper LO phase.	VEN ER 150 mg	**42Y M patient, on day 41** Self-harm (mild alcoholic intoxication) *"....He was randomly assigned to venlafaxine ER 150 mg/day on May 24, 1995. ...After temporary improvement of the depression, the patient relapsed (associated with mild alcohol intoxication) and was hospitalized from July 3 to July 19. During hospitalization a mild confusion and dissociative disorder (de-realization) were observed. Patient was discharged with good improvement. .. The patient discontinued the study on July 3...."*
0600B 1-384-US/EU /CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	VEN ER Dose unknown	**42Y M patient, on day 3** Suicide attempt with a kitchen knife **"***On 05 September 1999, the patient attempted to injure himself with a kitchen knife. The patient was hospitalized. As of 20 Sept 99, his condition had stabilized and he had no suicidal tendencies. He remained hospitalized for treatment of depression. No other information is available on this patient."*
0600B 1-384-US/EU /CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	IMI 125mg	**18Y M patient, on day 34.** Intentional Injury by cutting wrist *"On 05 December 1998, the patient intentionally cut his wrist. He was inebriated and disappointed in a love affair. The wounds were dressed and he was hospitalized in a psychiatric ward until 07 December1998."*
0600B 1-384-US/EU /CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI	PLB	**40Y F patient, on day 25/29** Intentional overdose on sleeping pills *"On 14 September 1998, the patient phoned the investigational site*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
				planned but was not followed strictly. The LO varied as well****		*and reported that she had taken "a bunch of sleeping pills" during the weekend of 29 Auust1998 in a suicide attempt. No treatment was noted." The day of event was noted as 25 in adverse event tables and 29 in the narrative."*
0600B 1-384-US/EU /CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	PLB	**40Y M patient, on day 17** Intentional overdose on PAR and Ibuprofen *"....On 08 October 98, the patient presented to an emergency room having reportedly taken 2 handfuls each of ibuprofen and paroxetine and 3 or 4 tablets of study drug.....The patient remained lucid throughout the event and had no sequelae. He was hospitalized until 30 Oct ober1998. He was discharged on paroxetine.*
0600B 1-384-US/EU /CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	PLB	**73Y F patient on day 36** Suicide attempt by stabbing at heart with a knife **"***On 25 March 1998, the patient stabbed herself below the heart with a pocket knife. The wound was 2 cm deep, with no signs of pleural or cardiac damage. The patient was treated surgically. Study drug was discontinued. After the event, the patient was described as well and stable."*
600A-:302-US, CA/30 2	July 1988	Aug. 1990	MDD	6 weeks The trial had a 7 ± 3 days of PLB LI and up to 6 days of taper LO	PLB	**19Y F patient, on day 5** Intentional overdose on unknown medication **"..***19-year-old woman in placebo arm took an intentional overdose of mother's medication on day 5. There was no history of suicidal ideation at entry into this trial, but 2-3 years earlier the patient had overdosed herself with "half a bottle" of Midol (medication for the relief of premenstrual syndrome)..."*

DLX: duloxetine; FLX: fluoxetine; IMI: imipramine; PAR: paroxetine; PLB: placebo; VEN: venaflaxine; VEN ER: venlafaxine extended release

FPFV: first patient, first visit; LPLV: last patient last visit; LI: lead-in phase of trial; LO: lead-out phase of the trial; EXT/ CONT: extension phase of the trial

Aug.: August; Jan: January; Dec.: December; Feb.: February; F: female; M: male; MDD: major depressive disorder; Nov.: November; OCD: obsessive compulsive disorder; Oct.: October; PT: post therapy; PTSD: posttraumatic stress disorder; Sept.: September; v: visit number; Y: years

*The HCJE FLX trial had a 9 week acute randomised phase (Study Period III and Study Period IV, where Study Period III was a double-blind adaptation period that lasted for 1 week and patients were randomized to receive either FLX 10 mg/day or PLB; and Study Period IV was a double-blind, fixed-dose acute treatment period that lasted for 8 weeks and patients were to FLX received 20 mg/day during this period or PLB). This was followed by an EXT/CONT phases: subchronic treatment phase and relapse prevention phase (Study Period V and Study Period VI, where Study Period V was a double-blind, non-responder re-randomization period that lasted for 10 weeks, responders at Visit 10 remained on fluoxetine 20 mg/day or PLB and FLX non-responders were re-randomized to either remain on FLX 20 mg/day or to receive fluoxetine 40 mg/day with an option to titrate to 60 mg/day. PLB non-responders remained on PLB; and Study Period VI was a double-blind, relapse prevention period that lasted for 32 weeks. FLX responders were re-randomized to either continue on the current FLX dose or PLB. PLB responders remained on PLB.
** The 329 PAR trial had no LO phase but clinical responders had treatment for 6 months with monthly visits. The non responders at the end of the 8-week study were withdrawn from the study and treated in an open-label manner.
*** There was no LO phase but patients who experienced a clinically significant improvement in their depressive syndrome were to be entered into a continuation study (Protocol 334C) with maintenance of their double blind medication for an additional 20 weeks. We did not have access to data from this phase of the study.
****The 0600B 1-384-US/EU/CA results state that PLB LI was for 3-11 days but 1 patient is listed as having only 1 day of LI. The LO planned was tapering of dose for 3 weeks, but only 1 week for Europe, however taper phase could be omitted or adjusted (up to 21 days in US and CA; 10 days in EU) if medically indicated. Data from 4-10 days after therapy was also noted.

Supplementary data Table 7 Number of suicide attempts (SA), (including intentional overdoses and intentional self-harm) in the lead-out or post therapy phase: 5 events in 5 patients, three on SSRIs (two on paroxetine and one on venlafaxine) and two on placebo.

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
701	March 2000	Jan. 2001	MDD paediatric	8 weeks Study had no PLB LI phase and up to 4 weeks of taper LO phase.	PAR 30mg	**15Y F patient, on day 53, 2 days after last dose** Suicide attempt by cutting open arm and intentional overdose on different Tylenol medications *"..The patient began receiving treatment with study medication on 28-April-2000. The patient began treatment at a dose of 10 mg/day and was titrated up, in 10 mg/week increments, to the highest dose of 30 mg on 18 May 2000. On l 7- June-2000 (Day 51), the patient*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
						received the last dose of study medication. On l 9- Jun-2000 (Day 53), two days after the last dose, the patient took 12 Extra Strength Tylenol® (paracetamol) and half a bottle of Tylenol Cold® tablets (chlorpheniramine/pseudoephedrine HCl/ dextromethorphan/ acetaminophen), and she also cut open her arm. The patient was hospitalized, placed in an intensive care unit, and underwent a stomach lavage. The patient was expected to be transferred to a psychiatric hospital. The patient was found to have low potassium and hemoglobin values. Treatment included prescription Paxil® (paroxetine/dose unknown), trazodone, and an iron supplement. The patient was considered withdrawn from the study because of this event. The overdose was reported to have resolved on l 9-Jun-2000, and the arm lacerations was reported to have resolved in Jul-2000...."
377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PLB	**14 Y F patient, on day 87 (during taper phase)** Intentional overdose on paracetamol *"...On 18 December 1997, the patient received her first treatment with study medication for depression. Approximately eighty seven days later, on 14 March 1998, the patient attempted suicide by the ingestion of paracetamol tablets (20 x 500mg) and was hospitalised.....and study medication was discontinued on 24 March 1998 at visit 10. The patient was reported to have recovered on 14 March 1998, but at the time of reporting, she remained hospitalised. ...the patient had just started the down titration phase of the study...."*
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	8 weeks Study had a 7 ± 10 days PLB LI and up to 3 days of taper LO phase.	PAR 20mg	**40Y F patient, 6 days after last dose** Intentional overdose on alprazolam *"...The current episode had started in September 1994. She was randomly assigned to receive paroxetine on April 15, 1995..... The patient took her last active dose of study medication on June 10, 1995, and completed the study on June 15....On June 2, she took 10 tablets of alprazolam 0.25 mg as a suicidal gesture. No specific action was taken.*
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	8 weeks Study had a 7 ± 10 days PLB LI and up	PLB	**38Y F patient, 10 days after last dose** Intentional overdose on zolpidem **"...***The current episode started in March 1995. She was randomly*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on the suicide attempts
				to 3 days of taper LO phase.		*assigned to receive placebo on May 25 1995..... The patient completed the study on July 23 1995. Her mood began to change on July 26 (Study day 63) related to a background of a sentimental break up. After visit 8 on August 2, she reported a suicide attempt by swallowing 10 tablets of Stilnox (IE 100 mg zolpidem). She was hospitalized on August 6 and was discharged on August 18 under Deroxat treatment....”*
0600B 1-384-US/EU /CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	VEN ER 210mg	**55Y M patient, 20 days after last dose** Intentional overdose on PAR *“On 20 August19 99, the patient took an overdose of 20, 20 mg paroxetine tablets. He was evaluated at a hospital and was not considered at risk from the overdose. Neither intervention nor hospitalization were needed. The patient was considered much improved when seen 2 weeks later as an outpatient.* The patient discontinued from study after 4 days on VEN ER therapy for reasons other than AE 8not stated what exactly), and the event occurred 20 days after last dose. This patient is only mentioned in the narratives, not the serious adverse event table listings or anywhere else in the CSR.

PAR: paroxetine; PLB: placebo; VEN: venaflaxine; VEN ER: venlafaxine extended release
FPFV: first patient, first visit; LPLV: last patient last visit; LI: lead-in phase of trial; LO: lead-out phase of the trial; EXT/ CONT: extension phase of the trial
Jan: January; F: female; M: male; MDD: major depressive disorder; Nov.: November; Oct.: October; PT: post therapy; Sept.: September; v: visit number; Y: years

Supplementary data Table 8 Number of suicidal ideation (SI) events in the pre-randomisation: 6 events in 6 patients, four events on duloxetine and two events on placebo

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
HMBC	March 2002	July 2003	MDD	26 weeks Study had an open label single arm LI phase with DLX prior randomisation and a 12 weeks rescue phase with either DLX 60 once daily or twice daily	DLX open label 60mg/ day	**49Y F patient, at v8 on day 75 (for 5 days)** Suicidal ideation (severe) ***"..... St****arted on open label duloxetine 60 mg QD, experienced the serious adverse event of suicidal ideation. The patient was started on open label duloxetine 60 mg QD on 9 October 2002. Upon screening the patient denied any alcohol abuse or dependence. On 22 December 2002 the patient called 911 as she had been drinking heavily. She was hospitalized in the inpatient mental health unit for suicidal ideation. ...She stated that 11 she wanted to drink herself into oblivion and didn't care if she ever woke up or not". ..She was discharged on 26-Dec-02. On 3 January 2003 the patient completed the open label phase of the study and was randomized to duloxetine 60 mg...".*
HMBC	March 2002	July 2003	MDD	26 weeks Study had an open label single arm LI phase with DLX prior randomisation and a 12 weeks rescue phase with either DLX 60 once daily or twice daily	DLX open label 60mg/ day	**24Y M patient, at v6 day on 45 (for 5 days) - Actual Term** Suicidal ideation (severe) *"...Started treatment on 2 July 2002. On 14 August 2002, the patient called the investigator to report a situational crisis due to family conflict. An emergency appointment was scheduled for 15 August 20 02. But in the early morning hours of 15 August the patient was hospitalized for suicidal ideation. The patient permanently discontinued study drug on this date. The patient's last dose of study drug was 14 August 2002....."*
HMBC	March 2002	July 2003	MDD	26 weeks Study had an open label single arm LI phase with DLX prior randomisation and a 12 weeks rescue phase with either DLX 60 once daily or twice daily	DLX open label 60mg/ day	**No patient details available, at v8 (exact day unknown)** Suicidal ideation (mild) The treatment emergent adverse event tables and serious adverse event tables within the main report listed 3 events of SI (for which narratives were available) and one mild event (for which no narrative and therefore no details were available). One mild SI event was noted at v8 from the appendix of all line listings of adverse events for all patients.
HMBC	March	July	MDD	26 weeks	DLX	**No patient details available, at v1 (exact day unknown)**

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
	2002	2003		Study had an open label single arm LI phase with DLX prior randomisation and a 12 weeks rescue phase with either DLX 60 once daily or twice daily	open label 60mg/ day	Suicidal thoughts (mild) The treatment emergent adverse event tables and serious adverse event tables within the main report listed 3 events of SI (for which narratives were available) and one mild event (for which no narrative and therefore no details were available). One event of mild suicidal thoughts was additionally noted event was noted at v1 for a different patient, from the appendix of all line listings of adverse events for all patients.
HMBOa	July 2001	March 2002	FM with or without MDD	1 week Study had 12 weeks acute randomised phase and no LO phase	PLB LI	**51Y F patient, at v1 (exact day unknown)** Suicidal thoughts (serious) *"....was not randomized to study drug in the study, experienced the serious adverse event of suicide risk due to major depressive disorder. The principal investigator considered the serious adverse event of suicide ideation as life threatening ....The patient came in for visit 1 on 06 December 2001. After performing part of the MINI, the patient was discontinued from the study due to high suicide risk. ...The principal investigator spoke with patient's personal physician. The personal physician requested that the patient be sent to the emergency room immediately for evaluation and follow-up. ..."*
HCJE	April 1998	July 2000	MDD paediatric	1 week PLB LI Study had 9 weeks acute randomised phase and no phase LO phase**	PLB LI	**16Y M patient, after v2 on day 2 of study** Suicidal thoughts (serious) *".....discontinued the study due to clinical findings of suicidal ideation, and was exclusionary according to protocol requirements. ....Patient was in the evaluation phase of the study and was hospitalized on 27-December-1998 for suicidal ideation. This event occurred after visit 2 but prior to the scheduled visit 3. Investigator discontinued patient from the study due to the serious suicidal risk, which is protocol exclusion number 20. ....Investigator discontinued patient from the study due to the serious suicidal risk...."*

DLX: duloxetine; PLB: placebo;
FPFV: first patient, first visit; LPLV: last patient last visit; LI: lead-in phase of trial; LO: lead-out phase of the trial
F: female; FM: Fibromyalgia; M: male; MDD: major depressive disorder; PT: post therapy; v: visit number; Y: years

* There were 533 patients on DLX for 12 weeks open label and this was followed by a total of 278 patients who continued the study and were randomised at v8 to either receive PLB (142) or DLX (136) for a further 26 weeks.
**The HCJE FLX trial had a 9 week acute randomised phase (Study Period III and Study Period IV, where Study Period III was a double-blind adaptation period that lasted for 1 week and patients were randomized to receive either FLX 10 mg/day or PLB; and Study Period IV was a double-blind, fixed-dose acute treatment period that lasted for 8 weeks and patients were to FLX received 20 mg/day during this period or PLB). This was followed by an EXT/CONT phases: subchronic treatment phase and relapse prevention phase (Study Period V and Study Period VI, where Study Period V was a double-blind, non-responder re-randomization period that lasted for 10 weeks, responders at Visit 10 remained on fluoxetine 20 mg/day or PLB and FLX non-responders were re-randomized to either remain on FLX 20 mg/day or to receive fluoxetine 40 mg/day with an option to titrate to 60 mg/day. PLB non-responders remained on PLB; and Study Period VI was a double-blind, relapse prevention period that lasted for 32 weeks. FLX responders were re-randomized to either continue on the current FLX dose or PLB. PLB responders remained on PLB

Supplementary data Table 9 Number of suicidal ideation (SI) events in the acute randomised phase: 63 in 62 patients,

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
HMBHa	Nov. 2000	May 2001	MDD	9 weeks The study had a merged screening and a gradual PLB LI (flexible time) phase and a gradual taper LO (flexible time) phase up to 2 weeks	DLX 60mg	**No patient details available, at v6 (exact day unknown)** Suicidal ideation (moderate) This event was not listed in any treatment emergent adverse event tables nor in the main text of the report and was only noted from the appendix of all line listings of adverse events for all patients.
HMBHa	Nov. 2000	May 2001	MDD	9 weeks The study had a merged screening and a gradual PLB LI (flexible time) phase and a gradual taper LO (flexible time) phase up to 2 weeks	DLX 60mg	**No patient details available, at v6-v9 (exact days unknown)** Suicidal ideation (moderate) This event was not listed in any treatment emergent adverse event tables nor in the main text of the report and was only noted from the appendix of all line listings of adverse events for all patients.

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
HMBHa	Nov. 2000	May 2001	MDD	9 weeks The study had a merged screening and a gradual PLB LI (flexible time) phase and a gradual taper LO (flexible time) phase up to 2 weeks	DLX Dose unknown	**No patient details available, at v4 (exact day unknown)** Increased suicidality (moderate) This event was not listed in any treatment emergent adverse event tables nor in the main text of the report and was only noted from the appendix of all line listings of adverse events for all patients.
HMBHb	Nov. 2000	May 2001	MDD	9 weeks The study had a merged screening and a gradual PLB LI (flexible time) phase and a gradual taper LO (flexible time) phase up to 2 weeks	DLX 60mg	**No patient details available, at v6 (exact day unknown)** Fleeting suicidal thoughts (moderate) This event was not listed in any treatment emergent adverse event tables nor in the main text of the report and was only noted from the appendix of all line listings of adverse events for all patients.
HMBHb	Nov. 2000	May 2001	MDD	9 weeks The study had a merged screening and a gradual PLB LI (flexible time) phase and a gradual taper LO (flexible time) phase up to 2 weeks	PLB	**No patient details available, at v1, v2-v6 (exact days unknown)** Thoughts of suicide (mild to moderate) This event was not listed in any treatment emergent adverse event tables nor in the main text of the report and was only noted from the appendix of all line listings of adverse events for all patients.
HMBHb	Nov. 2000	May 2001	MDD	9 weeks The study had a merged screening and a gradual PLB LI (flexible time) phase and a gradual taper LO (flexible time) phase up to 2 weeks	PLB	**No patient details available, at v1, v4-v8 (exact days unknown)** Occasional suicidal thoughts (moderate) This event was not listed in any treatment emergent adverse event tables nor in the main text of the report and was only noted from the appendix of all line listings of adverse events for all patients.
HMBHb	Nov. 2000	May 2001	MDD	9 weeks The study had a	PLB	**No patient details available, at v1, v4-v5 (exact days unknown)** Suicidal ideation (mild to moderate)

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
				merged screening and a gradual PLB LI (flexible time) phase and a gradual taper LO (flexible time) phase up to 2 weeks		This event was not listed in any treatment emergent adverse event tables nor in the main text of the report and was only noted from the appendix of all line listings of adverse events for all patients.
HMAYb	Oct. 2000	Jan. 2003	MDD	26 weeks This was the EXT/CONT phase of the trial after a 8 week acute phase with a 2 week PLB LO period	DLX 60mg	**32Y F patient, at v9 on day 77** Suicidal ideation (serious) *".....discontinued from the study due to the serious adverse event of worsening of depression on 3-May-2001, 84 days after randomization to duloxetine 60 mg BID for depression. The patient had one previous episode of major depression from June through August of 2000. The current episode of depression started in November of2000. The patient entered the study on 25-January 200l. The patient first reported worsening of depression on 26-April 200 I, 77 days after randomization. On 3-May-2001, the patient was hospitalized for the worsening of depressive symptoms. .....The patient's mood was reportedly labile but the depression improved and suicidal ideations disappeared during hospitalization. Last dose of duloxetine was 3-May-01, 84 days after randomization to blinded therapy.* This event was listed as 'worsening of depression' in the adverse event tables and the SI was only noted by the patient narrative, as it noted that "*suicidal ideations disappeared during hospitalization*", indicating that they existed before.
HMATa	March 2000	April 2001	MDD	8 weeks The study had a 1 week PLB LI and a 2 weeks PLB LO	DLX 20mg	**21Y F patient, at v4-v6 on day 6** Suicidal ideation (severe) **".....**discontinued from the study on 12-January-2001, 17 days after randomization to Duloxetine 20 mg BID, due to the adverse event of dissociation. The patient experienced an increasing sense of dissociative feelings for 5 days prior to discontinuation (dissociative feelings began 12 days after randomization) ....**S**evere suicidal urges began on 01- January-2001, 6 days after randomization, and continued through discontinuation. The patient stated that the dissociative feelings contributed to her suicidal thoughts....." No suicidal ideation was noted in tables and only in

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
						the patient narratives and the appendix of all line listings of adverse events for all patients.
HMATa	March 2000	April 2001	MDD	8 weeks The study had a 1 week PLB LI and a 2 weeks PLB LO	PAR 20mg	**No patient details available, at v6 (exact days unknown)** Suicidal ideation (mild) This event was not listed in any treatment emergent adverse event tables nor in the main text of the report and was only noted from the appendix of all line listings of adverse events for all patients.
HMATb	March 2000	Feb. 2001	MDD	8 weeks The study had a 1 week PLB LI and a 2 weeks PLB LO	PAR 20mg	**No patient details available, at v6 exact day unknown** Suicidal Ideation **(**moderate) This event was not listed in any treatment emergent adverse event tables nor in the main text of the report and was only noted from the appendix of all line listings of adverse events for all patients.
HMBC	March 2002	July 2003	MDD	26 weeks Study had an open label single arm LI phase with DLX prior randomisation and a 12 weeks rescue phase with either DLX 60 once daily or twice daily	DLX 60mg	**25Y F patient, at v13 on day 51** Threatened to harm oneself with a knife *"...On 22-Nov-02, 51 days after starting duloxetine (in R phase, or day 140 for 4 days), the patient experienced auditory hallucinations, increased depressive symptoms, and made suicidal threats. Early that AM, the patient threatened to harm herself while in the possession of a knife. The patient's partner reported that the patient had an increase in depressive symptoms due to psychosocial stressors that included loss of a job, denial of a loan application, and arguments with her family and partner. The patient was admitted to the hospital.....The patient reported her last dose of study drug was on 17-November-2002. On 25-Nov·-02 the patient was discharged from hospital. The adverse event of suicide threats resolved by 26-November-2002 and increased depressive symptoms resolved on 7-December-2002 but the event of auditory hallucination was still on-going at the patients last visit on 10-December 2002. The patient was discontinued from the trial on 10-December 2002 due to protocol violation."*
HCJE	April 1998	July 2000	MDD paediatric	9 weeks Study had 1 week PLB LI and no phase LO phase**	FLX 20mg	**13.26Y F patient, on day 70** Increased suicidal ideation *"..Parent (mother) phoned site to report patient was hospitalized on 12-April-1999 for suicidal ideation. Patient had a history of suicidal ideation with an onset of 8-November-1998, prior to study*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
						entry. Investigator decided to discontinue patient from study due to an increase in the patient's suicidal ideation. ....Patient had 70 days of study drug therapy at the time of discontinuation."
Protocol 377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PAR Dose unknown	**17Y F patient, on day 56** Suicidal risk "....experienced emotional lability and worsening depression and was considered a suicide risk. It lasted 25 days.."
Protocol 377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PAR Dose unknown	**15Y F, on day 23** Parasuicidal "...experienced emotional lability and was parasuicidal for one day"
Protocol 377	April 1995	May 1998	MDD paediatric	12 weeks Study had 2 weeks PLB LI and 2 weeks of taper LO phase.	PAR	**17Y M patient, on day 37** Suicidal intent "...On day 35 experienced severe irritability and nervousness considered possibly related to study drug. This was followed on day 37 by severe emotional lability with suicidal intent...."
Protocol 627	July 1998	Jan. 2000	PTSD	12 weeks Study had a 7 days PLB LI and up to 3 weeks of taper LO phase.	PLB	**34Y M patient, day 14** Suicidal ideation *"The patient received oral study medication (placebo dose level 1) from 22 September 1999. On Day 6 (27 September 1999), the patient experienced dizziness, lightheadedness, dyspepsia, insomnia and nausea (all moderate in intensity) all lasting 2 days except for the insomnia which continued beyond the end of the study, which all resulted in discontinuation of the study medication. The patient was withdrawn from the study the same day due to dyspepsia. ...No corrective therapy was given for these events. On 05 October 1999, some 8 days after the last dose, the patient experienced major depression including insomnia, loss of appetite, anergia, amotivation, diminished concentration, severe agitation, a sense of hopelessness and helplessness and suicidal ideation. The patient was reported not to have attempted suicide nor have a definite plan for the future. The patient was verbally aggressive on admission due to an alcoholic binge. According to the patient's wife he had*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
						been drinking heavily prior to his admission and was suffering from alcohol abuse, he had been verbally abusive and threatening towards her. ...”
Protocol 627	July 1998	Jan. 2000	PTSD	12 weeks Study had a 7 days PLB LI and up to 3 weeks of taper LO phase.	PLB	**29 Y Fpatient, on day 4** Suicidal ideation “*....The patient received oral study medication (placebo dose level 1) from 12 March 1999. Prior to the study the patient had experienced moderate worsening of depression (04 March 1999) lasting 5 days, moderate restlessness on 09 March 1999) which continued beyond the end of the study and moderate sleeplessness on 12 March 1999 which also continued beyond the end of the study. On 15 March 1999, four days after the first dose the patient developed a suicidal id*eation. *The patient refused to eat or drink and became socially withdrawn. ....Treatment with study medication was stopped due to the suicidal ideation on 15 March 1999 and the patient was withdrawn from the study the same day....”*
Protocol 627	July 1998	Jan. 2000	PTSD	12 weeks Study had a 7 days PLB LI and up to 3 weeks of taper LO phase.	PLB	**45Y M patient, on day 1** Suicidal ideation (mild) *“.....Concomitant medications included chloral hydrate from 18 June 1999 to 20 June 1999 for insomnia....The patient received study medication on 17 June 1999. The same day the patient experienced increased depression, tearfullness and mild suicidal ideation. The patient was hospitalised on 22 June 1999. ...Treatment with study medication was stopped due to a protocol violation on 17 June 1999....”*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
Protocol 701	March 2000	Jan. 2001	MDD paediatric	8 weeks Study had no PLB LI phase and up to 4 weeks of taper LO phase.	PAR 20mg	**11Y F patient, on day 20** Suicidal ideation *"...The patient began treatment with study medication on 06-September 2000. The patient began treatment at a dose of 10 mg/day and was titrated up to the highest dose of 20 mg on 13 September 2000. The last dose of blinded study medication was taken on 21 September 2000. On 25-Sep-2000 (Day 20), 19 days after the first dose, and 4 days after the last dose of study medication, the patient's mother called the investigator site to report that her daughter was admitted to the hospital for suicidal ideation. The patient had stated to her mother that she wanted to hang herself from the ceiling fan. The patient's mother thought that daughter was "attention seeking." No action was reportedly taken in regard to this event, but the patient was lost to follow-up...."*
Protocol 701	March 2000	Jan. 2001	MDD paediatric	8 weeks Study had no PLB LI phase and up to 4 weeks of taper LO phase.	PLB	**13 Y M patient, on day 5** Suicidality *"....The patient began therapy with study medication on 21-June-2000. On 26-June- 2000, 5 days later, the patient stole his parent's car and "wrecked it," and was hospitalized due to suicidal ideation. On 30-June-2000, the event was reported as resolved, and the patient was discharged from the hospital. It was reported that the patient was placed in a juvenile detention center. Treatment with study medication was stopped due to this event, and the patient was withdrawn from the study...."* This event was listed as a suicide attempt due to coding dictionary limitations in certain sections of the CSR for the verbatim term, but coded as emotional lability in the adverse event tables which was the preferred term in the coding dictionary.
Protocol 676	Nov. 1999	Oct. 2001	SAD/SP paediatric	16 weeks Study had no PLB LI phase and up to 4 weeks of taper LO phase.	PAR 40mg	**13Y F patient, on day 30** Suicidal thoughts *".....The patient received the first dose of study medication on 30 August 2000. The patient began treatment at dose level 1 (10 mg/day). The dose was increased to dose level 2 (20 mg/day) on 13 September 2000, to dose level 3 (30 mg/day) on 19 September*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
						2000, and to dose level 4 (40 mg/day) on 25 September, 2000, which continued throughout the remainder of the study. The last dose of study medication was taken on 02 October 2000 (Day 34). On 10 September 2000 (Day 12), the patient reported moderately severe myalgia (muscle discomfort), which was treated with ibuprofen and Tylenol® (paracetamol) and resolved in three days. The dose of study medication was increased in response to this condition. This event was considered to be unrelated to treatment with study medication. On 14 September, 2000 (Day 16), moderately severe agitation (panic attack) was reported. This cleared without treatment in one day and was considered to be probably unrelated to treatment with study medication. On 28 September 2000 (Day 30), the patient experienced severe agitation (panic attack worsening) lasting one day, which was considered by the investigator to be possibly related to treatment with study medication, and severely intense abnormal dreams (morbid thoughts) that were considered to be probably unrelated to treatment with study medication. In addition, moderately severe emotional lability (suicidal thoughts) was also reported to have begun on this date...."
Protocol 704	Jan. 2000	July 2001	OCD paediatric	10 weeks The study had no LI phase but up to 4 weeks taper LO phase	PAR 40mg	**15Y M patient, on day 25 (for 8 days)** Suicidal thoughts *"....On Day 25 of study medication, 1 day after reaching his maximum dose level, the patient began to have suicidal thoughts (preferred term: emotional lability) while staying at a youth shelter. He was hospitalized for evaluation, and, as a result of this event, study medication was stopped. ..."*
Protocol 329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	PAR 20mg	**14Y M patient, on day 14** Possible suicide thoughts *"....On l 7-November-1994, the patient received his first dose of study medication. On 30-November1994, the patient became very angry. He punched pictures, broke glass, and sustained lacerations that required six sutures. His anger subsided, but he expressed hopelessness and possible suicide thoughts. The patient was hospitalized due to his severe anger outburst and a worsening of his depression. ....Study medication was discontinued on this day...."*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
Protocol 329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	PAR 20mg	**14Y F patient, about 56 days** Saying one would kill oneself *".....On 07-March-1995, the patient received her first dose of study medication. As reported by the site, the patient began exhibiting symptoms of disinhibition, grandiosity, and expansive mood at around week four of the study. A clinical judgement was made by site medical staff to observe the patients behavior for the next one to two weeks for diagnostic and intervention planning. ...On 04-April 1995, the patient reported increased feelings of elation and expansive mood. There was also a decreased need for sleep, increased energy and an inflated self esteem. Other symptoms included accelerated speech, flight of ideas, motor hyperactivity. The school reported impulsive and sexually provocative behavior. Her behavior was closely monitored. On 02-May 95, the patient became agitated and said she would kill herself following threats of punishment from her mother to control her behavior. The patient was deemed a risk to herself and was brought to the crisis service. She was hospitalized on 02-May-95 and the decision was made that she would not enter the continuation phase...."*
Protocol 329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	PAR 20mg	**16Y F patient, on day 37** Suicidal ideation *"On 23-January-1997, the patient received her first dose of study medication. On 24-February-1997, the patient became more isolative, sleeping more and not attending to school. The study medication was discontinued on 24-February-1997 by the patient's mother without the knowledge of the study investigator or coordinator. The patient started Prozac the following day. Four days later, on 28-February1997, the patient did not sleep well all night, cried and experienced suicidal intentions. She was subsequently hospitalized for severe suicidal ideation..."* At the time of the SI event, the patient was on FLX rather than PAR.
Protocol 329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	IMI 200mg	**15Y F patient, on day 32** Suicidal ideation (moderate) *".....was randomized to imipramine 50mg/day on 30-January-1995. Dose was up-titrated to 200mg/day in 50mg/week increments*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
						by week 4. Study medication was stopped on day 32 because of suicidal ideation with gesture considered to be of moderate severity. ...”
Protocol 329	April 1994	Feb. 1998	MDD paediatric	8 weeks Study had no PLB LI phase and no LO phase**	PLB	**16/17 Y F patient, about 6 weeks** Suicidal thoughts *“....She commenced study medication on 04-January-1996. Approximately 6 weeks after commencing study 329, the patient experienced severe worsening of depression with severe suicidal thoughts. ....Study drug was stopped on 21-February-1996. The investigator reported that the worsening of depression and suicidal thought were life threatening ...Patient has a history of suicidal ideation without a definite plan. She has never had a suicide attempt...”* This event was coded as emotional lability (preferred term) in the adverse event tables.
Protocol 648	Feb. 1999	Feb. 2000	PTSD	12 weeks Study had 1 week LI and 2-3 weeks double blind tapering LO with a 2 week follow up PT	PAR Dose unknown	**37Y M patient, about 22 days** Suicidal thoughts *“.....entered R phase on 29-September-1999 & approx. 22 days later, on 21-October-1999, the patient was hospitalized with depression and suicidal thoughts. Study medication was discontinued on 21-October-1999 & the patient was started on Prozac (fluoxetine)...”* This event was coded as depression and emotional lability (preferred term) in the adverse event tables.
Protocol 651	Feb. 1999	Jan. 2000	PTSD	12 weeks Study had 1 week LI and 2 weeks of taper LO	PAR 40mg	**38Y F patient, on day 15** Suicidal Ideation “*....The patient's medical history includes a suicide attempt in August 1998 .....On 14-July-1999, the patient began treatment with blinded study medication for post traumatic stress disorder. Fourteen days later, on 28-July-1999, the patient had a routine study visit. At that time, the patient reported a recent breakup of a long-term relationship. The patient denied suicidal ideation at that time. The following day, on 29-Jul-1999, the patient was brought to the hospital by the county sheriff for suicidal ideation and for property damage. The patient was hospitalized for a 24 hour involuntary hold for observation. Treatment with study medication was stopped due to this event on 28-July-1999.....”.* No listing of suicidal ideations in main report. The event was coded as emotional

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
						lability (preferred term) in adverse event tables and the verbatim term in the narrative was suicide attempt, due to the dictionary.
Protocol 651	Feb. 1999	Jan. 2000	PTSD	12 weeks Study had 1 week LI and 2 weeks of taper LO	PAR 40mg	**46Y F patient, on day 26** Suicidal ideation/urges with a plan *"This case refers to a 46-year-old female ....Concomitant medications include chloral hydrate, cimetidine and loratadine. The patient took double-blind study medication for posttraumatic stress disorder from 25-Jun-1999 until 18-July-1999. The patient completed visit 4 with good compliance, and insomnia as an adverse event (non-serious). She did not keep her visit 5 appointment and was contacted by phone. She said that on 18-July-1999, she discontinued study medication due to persistent insomnia and anxiety. (Chloral hydrate had been helpful for sleep, but she had stopped it on 15-July-1999). On 20-July-1999, two days after stopping study medication, the patient consumed excessive alcohol, and while intoxicated, called a friend and asked if he would help her load a gun so she could kill herself as her PTSD symptoms were overwhelming. The friend stayed with her through the night, and she was without suicidal ideation/urges by the following day. The patient was seen on 05-Aug- 1999 for a termination visit and related the above story. She reported that she felt more anxious both on the study medication and for about one week after stopping it ....The event resolved by 21-Jul-1999."*
Protocol 651	Feb. 1999	Jan. 2000	PTSD	12 weeks Study had 1 week LI and 2 weeks of taper LO	PLB	**28Y F patient, about 54 days** Suicidal Ideation *".....On 24-March-1999, the patient began treatment with double-blind study medication for post traumatic stress disorder. Subsequently, the patient was involved in a pedestrian - automobile accident in which she was the pedestrian. Two days prior to her accident, she was fired from her job. After the accident, the patient reported an increase in anxiety, decreased self-worth, increase in intrusive thoughts about the accident and suicidal ideation. On 17-May-1999, 54 days after receiving the first dose of blinded study medication, the patient was evaluated and hospitalized in the medical-psychiatry unit. Study medication was discontinued on 16-May-1999....."*
R -	May	March	PTSD	12 weeks	SER	**27Y F patient, day unknown**

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
93ce21-0640	1994	1996		Study had 1week PLB LI phase and no LO phase	Dose unknown	Suicidal Ideation This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
R - 93ce21-0640	May 1994	March 1996	PTSD	12 weeks Study had 1week PLB LI phase and no LO phase	PLB	**40Y F patient, day unknown** Suicidal Ideation This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
R - 93ce21-0640	May 1994	March 1996	PTSD	12 weeks Study had 1week PLB LI phase and no LO phase	PLB	**27Y F patient, day unknown** Suicidal Ideation This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
R-93CE21-0641	May 1994	Sept. 1996	PTSD	12 weeks Study had 1week PLB LI phase and no LO phase	SER 25mg	**46 Y M patient, day 6** Suicidal Ideation *"....suicidal ideation, severe ....discontinued....resulting in hospitalization and resolving with treatment 7 days after last dose. Attributed to fiancée calling off marriage after finding out about subject's past."*
R-93CE21-0641	May 1994	Sept. 1996	PTSD	12 weeks Study had 1week PLB LI phase and no LO phase	SER Dose unknown	**29 Y F patient,** Suicidal Ideation (mild) This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
R-93CE21-0641	May 1994	Sept. 1996	PTSD	12 weeks Study had 1week PLB LI phase and no LO phase	SER Dose unknown	**37 F patient, about 87 days** Suicidal Ideation (mild) This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
R-93CE21-0641	May 1994	Sept. 1996	PTSD	12 weeks Study had 1week PLB LI phase and no LO phase	PLB	**30 Y F patient, on day 20** Suicidal Ideation (severe) This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative. This patient also reported severe depersonalization.
R-93CE21-	May 1994	Sept. 1996	PTSD	12 weeks	PLB	**47 Y M patient, on day 43** Suicidal Ideation

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
0641				Study had 1week PLB LI phase and no LO phase		"*..Started acute phase on 5th July 1994 and on 7/5/94 was upset because his check had not come and because of a meeting with other veterans. He mentioned suicidal ideation to a worker at the subject's homeless shelter and was sent to the emergency room. He was admitted to the hospital, where he denied suicidal intent. He was released from the hospital after three days, and completed the study on 8/15/94*"
R-93CE21-0641	May 1994	Sept. 1996	PTSD	12 weeks Study had 1week PLB LI phase and no LO phase	PLB	**51 Y M patient, on day 8** Suicidal Ideation (mild) This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative. The patient continued and completed the study.
90CE21-0498	Dates unknown	Dates unknown	OCD paediatric	12 weeks Study had 1week PLB LI phase and no LO phase	PLB	**No details available on patient, day unknown** Suicidal Ideation (mild) This event was only noted in the treatment emergent adverse event tables and no further information is available on this event.
R-0601	Jan. 2000	May 2001	GSP	12 weeks Study had 7 to 14 days of PLB LI phase and up to 2 weeks of taper LO phase	SER Dose unknown	**No details available on patient, day unknown** Suicidal Ideation (mild) This event was only noted in the treatment emergent adverse event tables and no further information is available on this event.
050-336	Nov. 1992	Sept. 1994	OCD	12 weeks Study had 7 to 14 days of PLB LI phase and no LO phase	SER 50mg	**36 Y F patient on day 7** Potentially suicidal "*....patient experienced mood swings and was potentially suicidal...other adverse events include: apathy, emotional lability, fatigue*.."
STL-NY-94-004	March 1996	Oct. 1997	SP	20 weeks Study had 1week PLB LI phase and unclear whether any LO or drug free period exits, but some could enter an EXT	PLB	**50 Y M patient, on days 126-140 and still present on last day of follow-up** Suicidal Ideation (moderate) This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
				trial		
93CE21-0629	April 1994	April 1995	PD	10 weeks Study had 2weeks PLB LI phase and no LO phase	PLB	**No age available , F patient, day unknown** Suicidal Ideation (mild) This event was only noted in the treatment emergent adverse event tables and no further information is available on this event.
A0501001	Dec. 1999	May 2001	MDD paediatric	10 weeks Study had no PLB LI phase and no LO phase	SER 50 mg	**10Y M patient, on days 21-26** Suicidal ideation "*....Twenty-one days after starting sertraline, on 09 November 2000, he was involved in an argument with his teacher and he made a comment suggestive to the teacher of suicidality. The school social worker was not immediately available to assess the child so ...the subject hospitalized. His attending physician saw no evidence of suicidality and he was discharged from the hospital on 14 November 2000. The subject was permanently discontinued from the study....*"
A0501001	Dec. 1999	May 2001	MDD paediatric	10 weeks Study had no PLB LI phase and no LO phase	SER 100mg	**12Y M patient, on days 56-62** Suicidal ideation "*....The subject developed worsening symptoms of major depressive disorder on 12 July 2000 and expressed suicidal ideation on 19 July 2000. Because the subject could not contract for safety, the investigator decided to hospitalize the subject. Duration of sertraline therapy up to the event was 55 days. The subject was taking 100 mg/day of sertraline at the time of the event. The subject has a past psychiatric history of suicidal ideation. ... He was taking no concomitant medications prior to the event. The subject was permanently discontinued from the study due to worsening of the subject's major depressive disorder....*"
237/248 (80ce21-0237 and 86ce21-0248)	Dates unknown	Dates unknown	OCD	8 weeks The study had a 1 week PLB LI phase and a 2 week taper LO phase	PLB	**No details on patient available, on day 26** Suicidal ideation (severe) "*Patient .....experienced severe suicidal ideation after 26 days of placebo treatment. This event is classified as "suicide attempt" according to WHO terminology.... although an actual gesture or attempt did not occur. The patient was discontinued from the study 4 days after onset of suicidal ideation, although the investigator discontinued the patient due to "insufficient, clinical response"*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
						rather than any adverse experience. The suicidal ideation resolved 6 days after study discontinuation (10 days after onset) and has not recurred..."
371/372 SHORT (88CE21-0371/ 0372 (12 weeks)	Dates unknown	Dates unknown	OCD	12 weeks Study had 1 week PLB LI phase and completers continued in a EXT/CONT phase	SER 200mg	**33Y M patient, on day 78** Suicidal ideation (severe) *"...severe suicidal ideation secondary to acute depression....Patient hospitalized. Suicidal ideation resolved after 1 day's duration. Patient had history of depression pre-dating study* This event was listed as inter-current illness rather than within the adverse events tables.
600A-313-US	May 1989	June 1990	MDD	6 weeks	VEN 25mg	**19YM patient, on day 21** Suicidal ideation "*..A 19-year-old man was enrolled on July 19, 1989, with a 34-week history of major depression and anxiety attacks. He had suicidal thoughts prior to enrolment. He was randomly assigned to treatment with venlafaxine 25 mg/d and showed some improvement. However, he was withdrawn prematurely on day 22 (August 9, 1989) because the depression returned. The depression, including suicidal ideation, was similar to that seen at the pre-study evaluation....*" This event was noted as depression in the adverse event tables and only noted as depression with suicidal ideation from the patient narrative.
600A-313-US	May 1989	June 1990	MDD	6 weeks The study had a 7 ± 3 days of PLB LI and within 72 hours of completion, patients could elect to enrol in an EXT trial (protocol 600A-314-US)	PLB	**35Y F patient, on day 7** Suicidal thoughts *"...This 35-year-old woman enrolled on April 26, 1990. She had a history of 2 suicide attempts, in 1967 and in the mid-1970s, as well as current suicidal ideation. She was randomly assigned to placebo but was withdrawn 7 days later because of worsening of the depression and increasing suicidal thoughts...."* This event was noted as worsened depression in the adverse event tables and only noted as depression with suicidal ideation from the patient narrative.
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	8 weeks The study had a 7 ± 10 days f PLB LI and	VEN ER 150mg	**42Y F patient, on day 58** Suicidal obsessions (severe) This event was only noted in the all adverse event listings and no

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
				up to 3 days of taper LO phase		further information is available as there was no patient narrative.
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	8 weeks The study had a 7 ± 10 days f PLB LI and up to 3 days of taper LO phase	PAR 20mg	**58Y M patient**, **on day 29**, Anxiety/suicidal thoughts *"...This 58-year-old male patient was screened for suitability for the study on February 16, 1995 and was randomly assigned to receive paroxetine on February 23, 1995..... On March 23... the patient was admitted to hospital. He presented with severe psychomotor retardation with disruption of diurnal/nocturnal patterns and with severe anxiety, feelings of worthless and suicidal thoughts.....The patient was discontinued from the study at the time of hospitalization on March 23..."*
0600B 1-384-US/EU/ CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	IMI	**42Y F patient, on day 11.** Suicidal ideation This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
0600B 1-384-US/EU/ CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	IMI	**56Y F patient , on day 14** Depression and suicidal ideation This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
0600B 1-384-US/EU/ CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	IMI	**31Y F patient, on day 2** Suicidal ideation This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
0600B 1-384-	Sept. 1997	Nov. 1999	MDD	6 weeks	PLB	**58Y F patient, on day 13** Suicidal ideation

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
US/EU/ CA				The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****		This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
0600B 1-384-US/EU/ CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	PLB	**39Y M patient, on day 4** Black ideas (suicidal thoughts): Moderate "*On 7 Sep 98, the patient was hospitalized because of suicidal ideation."*
0600B 1-384-US/EU/ CA	Sept. 1997	Nov. 1999	MDD	6 weeks The trial had a 7 ± 4 days of PLB LI planned but was not followed strictly. The LO varied as well****	PLB	21Y F patient, on day 25 Increasing suicidal thoughts "*On 25 Mar 98, the study drug was discontinued because of severe anxiety and increasing suicidal thoughts. Because of the severe risk to the patient, the study code was broken. It was found that the patient had been assigned placebo. The patient was hospitalized and Effexor therapy was begun."*
0600A1-372-US	Sept. 1995	June 1997	MDD	6 weeks The trial had a 7 ± 3 days of PLB LI and up to 3 weeks of taper LO	PLB	**45Y M patient, on day 34** Increased suicidal ideation *"This 45-year-old man was randomly assigned to receive placebo on 12 December 1995. On 14 January 1996, study day 34, he reported increased suicidal ideation for the previous 2 days after receiving a very poor evaluation at work. The patient was hospitalized and study drug treatment was discontinued. He was hospitalized for 4 days and his suicidal ideation resolved. He began receiving antidepressant therapy...."*
0600B-209-US	Dec. 1994	Aug. 1995	MDD	8 weeks The trial had a 7 ± 3 days of PLB LI and up to 2 weeks of taper LO	PLB	**36Y F patient, on day 12 and day 39 (2 events)** Suicidal ideation (severe) *"This 36-year-old woman was randomly assigned to receive placebo on 2 March 1995. On 14 March 1995, study day 13, the patient developed suicidal ideation and study drug treatment was*

Trial	Start date FPFV	End date LPLV	Condition	Duration of acute phase	Drug and daily dose	Case notes on suicidal ideation
						discontinued. The patient was hospitalized on 15 March 1995. The patient received ECT therapy and was discharged from the hospital on 6 April 1995 on imipramine and Klonopin. The patient was readmitted to the hospital on 10 April 1995 because of suicidal ideation."

DLX: duloxetine; IMI: imipramine; PAR: paroxetine; SER: sertraline; VEN: venaflaxine; VEN ER venaflaxine extended release; PLB: placebo
Aug.: August; Feb.: February; Dec.; December; GSP: generalized social phobia; Jan.: January; MDD: major depressive disorder; Nov.; November; OCD: obsessive compulsive disorder; Oct.: October; PD: panic disorder; PTSD: posttraumatic stress disorder; SAD: social anxiety disorder; Sept.: September; SP: social phobia

Supplementary data Table 10 The number of suicidal ideation (SI) events in lead-out (LO) or post therapy (PT): 7 events in 7 patients, all on SSRIs (one on duloxetine, three on paroxetine, two on sertraline and one on venlaflaxine).

Trial	Start date FPFV	End date LPLV	Condition	Study duration	Drug and daily dose	Case notes on suicidal ideation
HMATb	March 2000	Feb. 2001	MDD	During LO The study had an 8 weeks acute phase and a 2 weeks PLB LO phase	DLX 20mg	**No patient details available, at v9 (exact day is unknown)** Passive suicidal ideation This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
Protocol 329	April 1994	Feb. 1998	MDD paediatric	Post therapy Study had an 8 weeks acute phase and no PLB LI phase and no LO phase	PAR Dose unknown	**15Y F patient, about 111 days from start of study (exact number of days post treatment is unknown)** Threatened suicide "*....On 27-June-1995, the patient received her first dose of study medication. On 15-September-1995, the patient had to be hospitalized after an argument. She had become combative with her mother and had threatened suicide. She was prescribed Zoloft. Several days before her hospitalization, she had not taken her study medication. At the time of discharge, the patient was experiencing some depressive symptoms. In the opinion of the investigator, the event was probably not related to the study medication but to the parent's primary condition and family problems...."*

Trial	Start date FPFV	End date LPLV	Condition	Study duration	Drug and daily dose	Case notes on suicidal ideation
Protocol 651	Feb. 1999	Jan. 2000	PTSD	Post therapy Study had 12 weeks of acute phase with 2 weeks of taper LO	PAR 20mg	**27Y F patient, 13 days after last dose** Suicidal ideation with a plan, auditory hallucinations *"...This report refers to a 27-year-old female....On 04-August-1999, the patient received the first dose of blinded study medication for Posttraumatic Stress Disorder (PTSD). On 24-0ctober-1999, the patient discontinued use of blinded study medication on the recommendation of her primary care physician who had prescribed Norflex (orphenadrine citrate), codeine, Flexaril (cyclobenzaprine hydrochloride, and Valium (diazepam) for back pain. This event is cited on the patient's case report form as an adverse experience leading to withdrawal from the study. She missed her visit 8 appointment scheduled for 27-0ctober-1999 and missed the rescheduled appointment on 29-0ctober-1999. On 02-November-1999, 90 days after receiving the first dose of medication, and 13 days after discontinuing study medication, the patient's husband called the site and reported that the patient was experiencing a "panic attack" after a family argument. He stated that the patient was "hearing voices again." The patient expressed suicidal ideation with a plan, and verbalized that the voices told her "to take all the pills in the house." The patient was admitted to a hospital later that evening...."*
Protocol 627	July 1998	Jan. 2000	PTSD	Up to 3 weeks of double blind tapering LO phase, followed by 14 days PT (but could range from 2 to 6 weeks PT) The trial had a 1 week PLB LI and an acute phase of 12 weeks.	PAR	**41Y F patient, 6 days after last dose.** Suicidal ideation *"....The patient had a history of depression and anxiety. The patient received oral study medication from 25 September 1999 until 14 December 1999. On 20 December 1999, some 6 days after the last dose, the patient experienced insomnia, loss of appetite, anergia and disinterest. Later, the patient also experienced amotivation, poor concentration, negative and pessimistic thoughts, hopelessness and thoughts of death. Relevant tests included a computed tomography scan which was normal. The patient was diagnosed as having worsening major depression and suicidal ideation. The patient was treated for the event with paroxetine, alprazolam and zopiclone. Each of these events lasted 37 days. The investigator considered this to be a serious event because it was life threatening, disabling,*

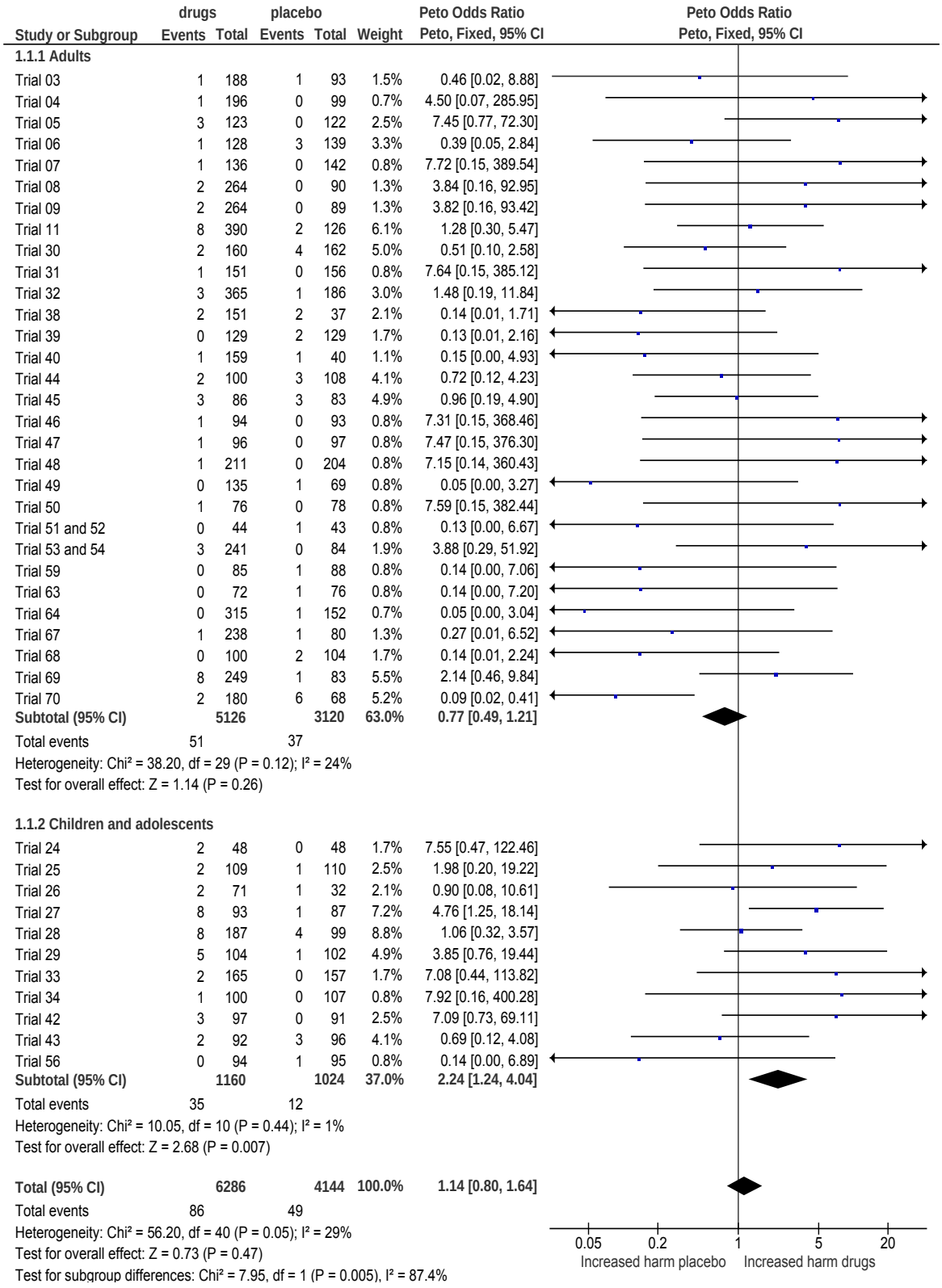
Trial	Start date FPFV	End date LPLV	Condition	Study duration	Drug and daily dose	Case notes on suicidal ideation
						incapacitating and resulted in hospitalisation." This event was noted as worsening depression and only clarified as a SI through the patient narrative.
95CE21-0671	May 1996	June 1997	PTSD	No LO phase The study had 2weeks PLB LI phase and 12 weeks of acute therapy	SER	**47Y F patient, 17 days after last dose** Suicidal ideation (mild) This event was only noted in the all adverse event listings and no further information is available as there was no patient narrative.
R - 96ce21-0682	July 1996	Jan. 1998	PTSD	No LO phase The study had a 2 week PLB LI phase and 12 weeks of acute phase	SER 20mg	**24Y F patient, about 11 days after last dose and on day 95 of study** Threatened suicide by stabbing with a knife *"...patient started randomised therapy on sertraline with 25 mg daily on 5/21/97. Dosage was titrated until reaching 200 mg daily beginning 6/16/97 and remained at that until completing the study on 8/12/97. On 8/23/97, the subject threatened to commit suicide and attempted to stab herself with a knife. The subject was admitted to the hospital as a precautionary measure, and was treated with sertraline beginning 8/24/97. The suicidal ideation resolved on 8/27/97...."*
0600B-367-EU	Oct. 1994	Sept. 1995	MDD	Post therapy The study had a 7 ± 10 days f PLB LI with 8 weeks of acute phase and up to 3 days of taper LO phase	VEN 75mg	**28Y M patient, 4 days after last dose** Suicidal feeling *"This 28-year-old male patient was screened for his suitability for the study on May 31, 1995 and was randomly assigned to receive venlafaxine ER 75 mg/day on June 7, 1995. ...on August 10, the patient reported that he was feeling suicidal. This was after having been fired from work and therefore these feelings were not considered study drug related by the investigator. The patient completed the study and took his last dose of active study medication on August 6."*

DLX: duloxetine; IMI: imipramine; PAR: paroxetine; SER: sertraline; VEN: venaflaxine; VEN ER venaflaxine extended release; PLB: placebo

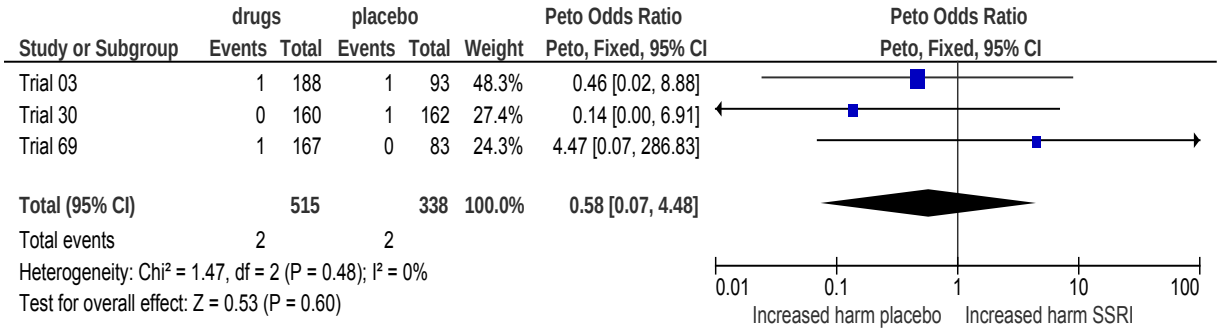
Aug.: August; Feb.: February; Dec.; December; GSP: generalized social phobia; Jan.: January; MDD: major depressive disorder; Nov.; November; Oct.: October; PTSD: posttraumatic stress disorder; Sept.: September

Supplementary Data D: Additional analyses

1. Meta-analysis of suicidality events (rather than patients) on SSRIs or SNRIs compared to placebo post randomisation



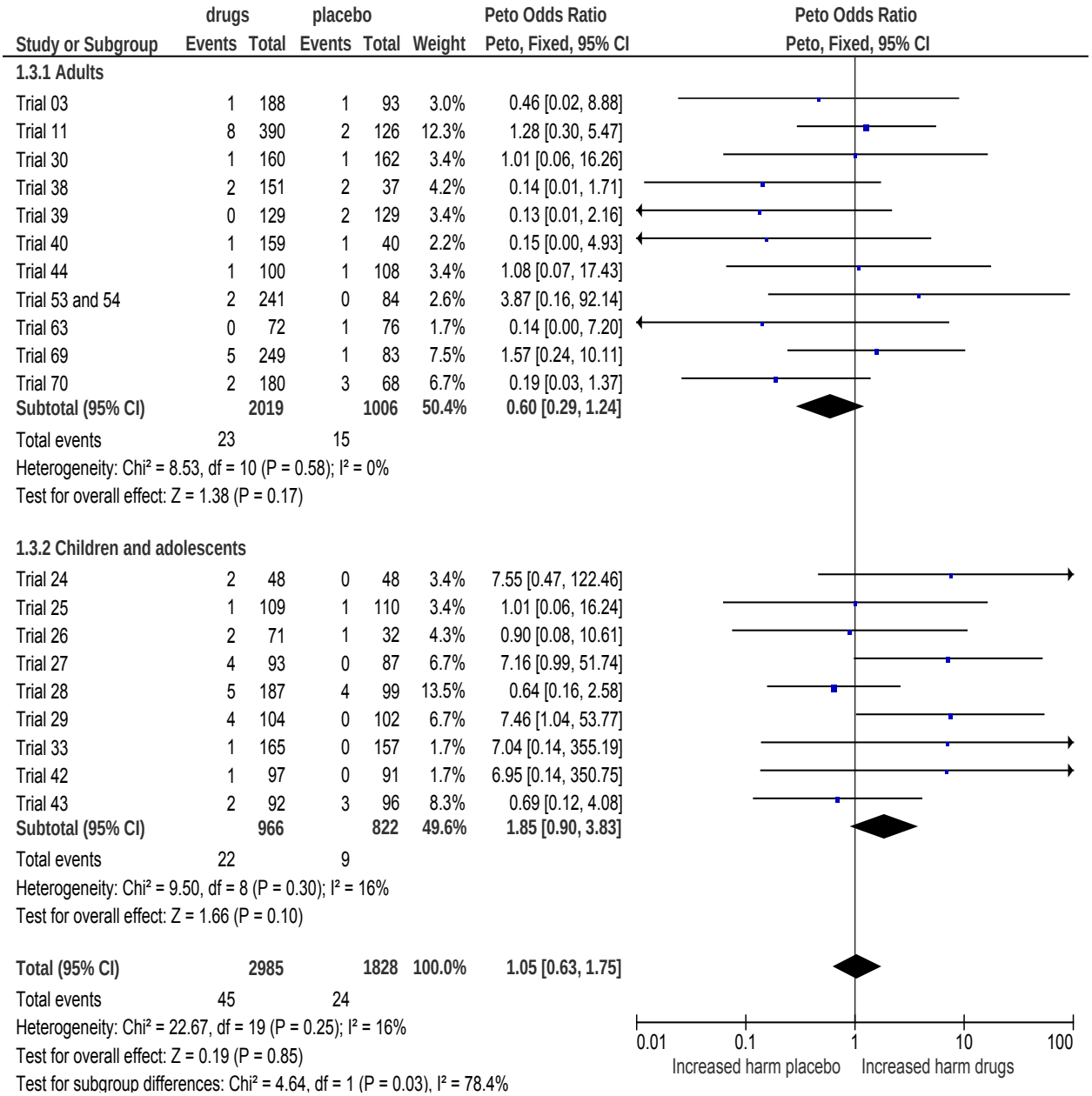
2. Meta-analysis of suicides on SSRIs or SNRIs compared to placebo post randomisation



Study or Subgroup	drugs Events	Total	placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Trial 03	1	188	1	93	48.3%	0.46 [0.02, 8.88]
Trial 30	0	160	1	162	27.4%	0.14 [0.00, 6.91]
Trial 69	1	167	0	83	24.3%	4.47 [0.07, 286.83]
Total (95% CI)		**515**		**338**	**100.0%**	**0.58 [0.07, 4.48]**
Total events	2		2			

Heterogeneity: Chi² = 1.47, df = 2 (P = 0.48); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)

3. Meta-analysis of suicides and suicide attempts only (no ideation) on SSRIs or SNRIs compared to placebo post randomisation



Study or Subgroup	drugs Events	Total	placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.3.1 Adults						
Trial 03	1	188	1	93	3.0%	0.46 [0.02, 8.88]
Trial 11	8	390	2	126	12.3%	1.28 [0.30, 5.47]
Trial 30	1	160	1	162	3.4%	1.01 [0.06, 16.26]
Trial 38	2	151	2	37	4.2%	0.14 [0.01, 1.71]
Trial 39	0	129	2	129	3.4%	0.13 [0.01, 2.16]
Trial 40	1	159	1	40	2.2%	0.15 [0.00, 4.93]
Trial 44	1	100	1	108	3.4%	1.08 [0.07, 17.43]
Trial 53 and 54	2	241	0	84	2.6%	3.87 [0.16, 92.14]
Trial 63	0	72	1	76	1.7%	0.14 [0.00, 7.20]
Trial 69	5	249	1	83	7.5%	1.57 [0.24, 10.11]
Trial 70	2	180	3	68	6.7%	0.19 [0.03, 1.37]
Subtotal (95% CI)		**2019**		**1006**	**50.4%**	**0.60 [0.29, 1.24]**
Total events	23		15			
Heterogeneity: Chi² = 8.53, df = 10 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.38 (P = 0.17)						
1.3.2 Children and adolescents						
Trial 24	2	48	0	48	3.4%	7.55 [0.47, 122.46]
Trial 25	1	109	1	110	3.4%	1.01 [0.06, 16.24]
Trial 26	2	71	1	32	4.3%	0.90 [0.08, 10.61]
Trial 27	4	93	0	87	6.7%	7.16 [0.99, 51.74]
Trial 28	5	187	4	99	13.5%	0.64 [0.16, 2.58]
Trial 29	4	104	0	102	6.7%	7.46 [1.04, 53.77]
Trial 33	1	165	0	157	1.7%	7.04 [0.14, 355.19]
Trial 42	1	97	0	91	1.7%	6.95 [0.14, 350.75]
Trial 43	2	92	3	96	8.3%	0.69 [0.12, 4.08]
Subtotal (95% CI)		**966**		**822**	**49.6%**	**1.85 [0.90, 3.83]**
Total events	22		9			
Heterogeneity: Chi² = 9.50, df = 8 (P = 0.30); I² = 16%						
Test for overall effect: Z = 1.66 (P = 0.10)						
Total (95% CI)		**2985**		**1828**	**100.0%**	**1.05 [0.63, 1.75]**
Total events	45		24			
Heterogeneity: Chi² = 22.67, df = 19 (P = 0.25); I² = 16%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Test for subgroup differences: Chi² = 4.64, df = 1 (P = 0.03), I² = 78.4%						

4. Fraudulent behaviour:

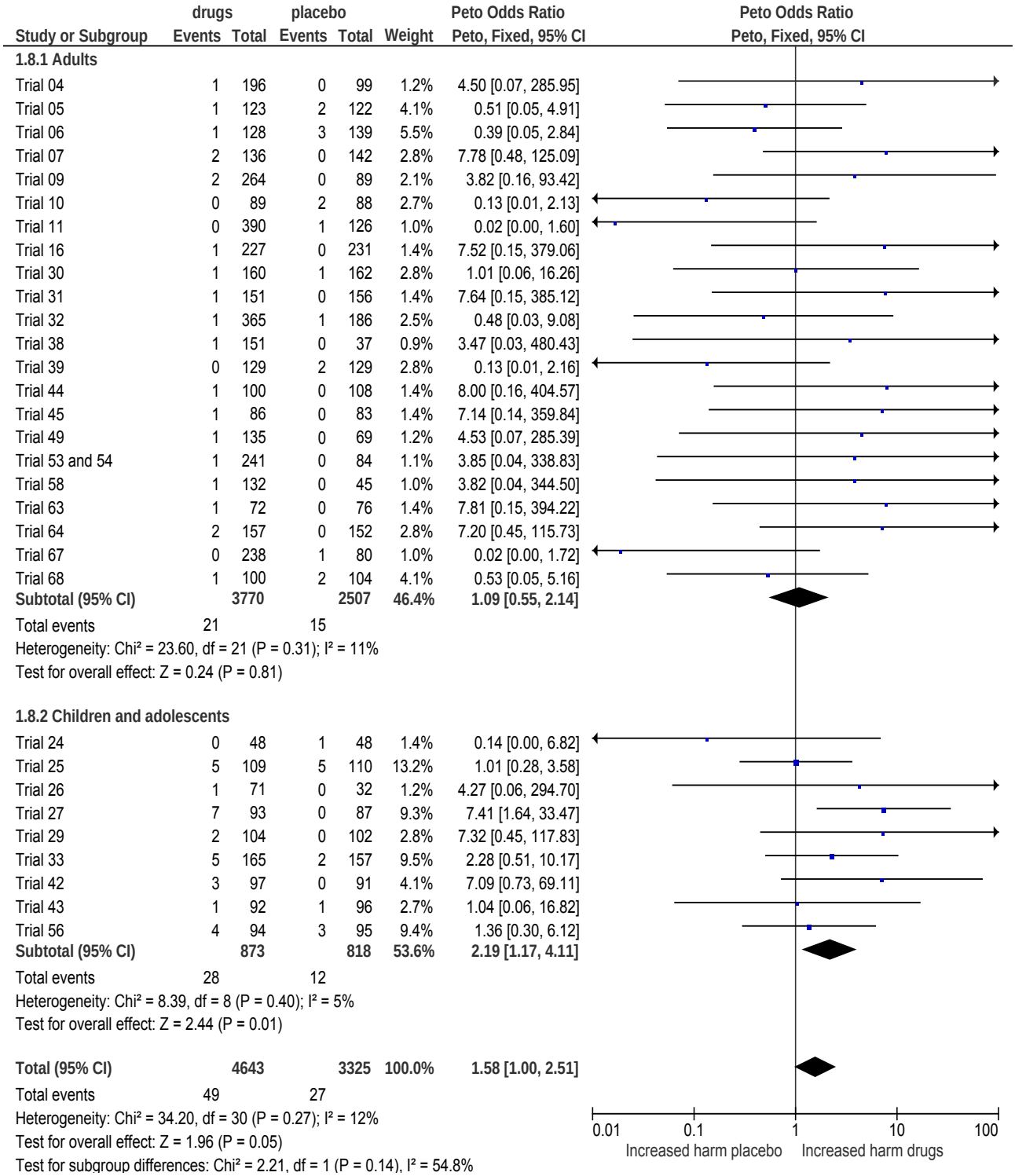
The drug companies had concerns about the validity of the data or fraudulent behaviour in some centres, in 3 trials:

- Trial 28 (paroxetine protocol 377) - The centre identified for fraudulent behaviour was 7. There were no deaths in this trial and none of the 8 patients with suicidality events on paroxetine (centres 9, 11, 30, 42(3), 49, and 53), nor the 4 on placebo (centres 5, 10, 29, 41), were from that centre. This trial also had 3 aggressive behaviour events on paroxetine, but as we did not have the individual data, could not identify which centres they were from.

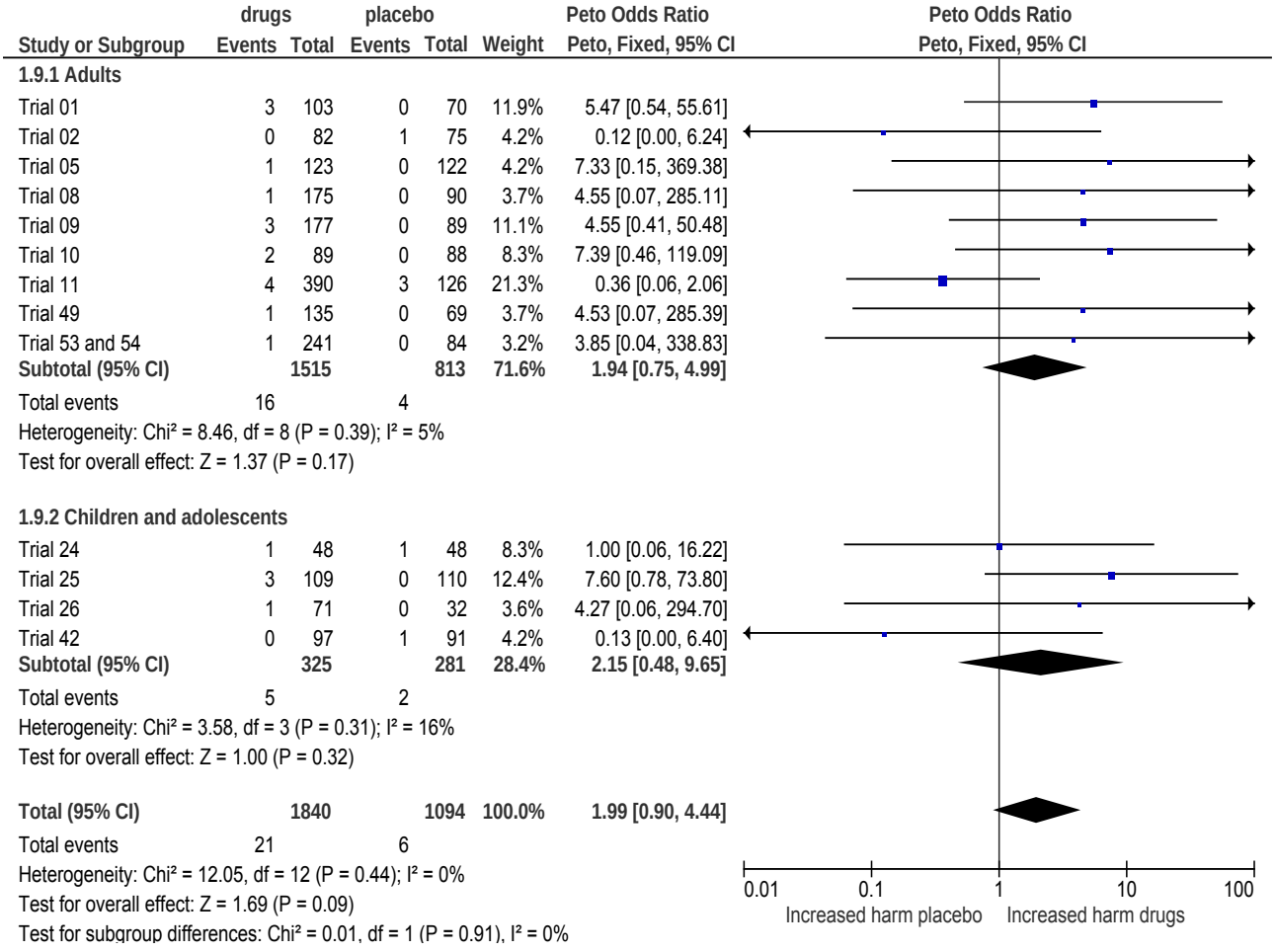
- Trial 34 (paroxetine protocol 704) - The centre identified for fraudulent behaviour was 5. There were no deaths in this trial and the one suicidal ideation event on paroxetine was a patient from centre 33. This trial also had 10 aggressive behaviour events on paroxetine and one on placebo, but as we did not have the individual data, could not identify which centres they were from.

- Trial 70 (venlaflaxine extended release 0600B 1-384-US/EU/CA) - The centres identified for fraudulent behaviour were 33, 34, 35 and 36 and for centres 33, 34, 35 no adverse event data was included: "*Since all source documentation and CRF case books were impounded before patient data could be reviewed, it was determined that only the available adverse event records from these sites would be reviewed for safety. The medical monitor determined that no unexpected adverse events or serious adverse events were identified.*" For centre 36, only efficacy data was not included. Two deaths were noted for this trial but were from centres 66 (imipramine) and 52 (venlaflaxine extended release). There were 6 patients on placebo (centres 20, 23, 25, 37, 46 and 52) and 2 on venlaflaxine extended release (centres 20 and 66) that had suicidality events, so once again not from centres with concerns.This trial also had one akathisia event on venlaflaxine extended release but as we did not have the individual data, could not identify which centre that was from.

4a. Meta-analysis of aggressive behaviour events excluding trials (28 and 34) with fraudulent behaviour



4b. Meta-analysis of akathisia events excluding trial (70) with fraudulent behaviour



5. Comparison of our data with the online summary trial reports on Eli Lilly's website

Drug: duloxetine				
Trial No.	**Trial Name**	**Relevant Outcomes**	**From clinical study report (CSRs)**	**From Lilly website online summary reports**
1.	HMAQa	akathisia	3 events on duloxetine	Missing
2.	HMAQb	akathisia	1 event on placebo	Missing
3.	HMAYa	mortality	2 deaths on duloxetine and 1 on placebo	2 deaths on duloxetine and 1 on placebo also noted
		suicidality	1 suicide on duloxetine and 1 on placebo	1 suicide on duloxetine and 1 on placebo also noted
4.	HMAYb	suicidality	1 suicidal ideation on duloxetine	Missing
		aggressive behaviour	1 event on duloxetine	Missing
5.	HMBHa	suicidality	3 suicidal ideation events on duloxetine	Missing
		aggressive behaviour	1 event on duloxetine and 2 events on placebo	Missing
		akathisia	1 event on duloxetine	Missing
6.	HMBHb	suicidality	1 suicidal ideation event on duloxetine and 3 suicidal ideation events on placebo	Missing

Drug: duloxetine				
Trial No.	**Trial Name**	**Relevant Outcomes**	**From clinical study report (CSRs)**	**From Lilly website online summary reports**
		aggressive behaviour	1 event on duloxetine and 3 events on placebo	Missing
7.	HMBC	mortality	1 death on duloxetine (prior to randomisation)	Missing (report only available from randomisation phase not the 12 week open label treatment with duloxetine)
		suicidality	1 suicide (prior to randomisation) and 1 suicidal ideation event both on duloxetine	Missing (report only available from randomisation phase not the 12 week open label treatment with duloxetine)
		aggressive behaviour	2 events on duloxetine	Missing
8.	HMATa	mortality	1 death on duloxetine	1 death on duloxetine also noted
		suicidality	1 suicidal ideation event on duloxetine and 1 on paroxetine	Missing
		akathisia	1 event on duloxetine	Missing
9.	HMATb	suicidality	1 suicidal ideation event on duloxetine and 1 on paroxetine	Missing
		aggressive behaviour	2 events on duloxetine	Missing
		akathisia	3 events on duloxetine	Missing
10.	HMAH	suicidality	No suicidality outcomes detected. No events noted, as accidental overdoses were not included in our study. From the CSRs we can see that though there were 9 patients with overdoses on duloxetine (5 in the main phase of the trial and 4 additional cases in the extension phase) and 8 on placebo (4 in each phase), they were all accidental *(*e.g. on day 12 a 30 year old female on duloxetine *"took two doses on same day; patient accidently dosed twice in the same day. The first dose was at 19:15 and the second dose was at 21:08. No AE's reported as result)".*	9 patients on duloxetine and 8 patients on placebo took overdoses. The report does not distinguish between accidental overdoses and intentional overdoses. We took the conservative approach and did not include any accidental overdoses in our study.
		aggressive behaviour	2 events on the same placebo patient noted.	2 events on placebo also noted.
		akathisia	2 events on duloxetine	Missing
11.	HMAI	suicidality	8 suicide attempts in 7 patients on duloxetine and 2 on placebo From the CSR we can see that 5 patients on duloxetine had 'suicide attempts' and 2 patients had intentional overdoses listed (with one patient having 2 events). There was 1 intentional injury on placebo and 1 suicide attempt.	Only 2 events of intentional overdose and 4 suicide attempts on duloxetine listed. No events on placebo listed.
		aggressive behaviour	1 event on placebo	Missing
		akathisia	4 events on duloxetine and 3 on placebo	Missing
12.	HMAG	none	No primary nor secondary outcomes detected	2 patients on placebo took overdoses. The report does not distinguish

Drug: duloxetine				
Trial No.	**Trial Name**	**Relevant Outcomes**	**From clinical study report (CSRs)**	**From Lilly website online summary reports**
			No events noted, as accidental overdoses were not included in our study. From the CSRs we can see that the two patients on placebo (64 year old man and 45 year old woman) had accidental overdoses, they both took two tablets instead of one at 12 weeks and 11 weeks respectively.	between accidental overdoses and intentional overdoses. We took the conservative approach and did not include any accidental overdoses in our study.
13.	SBAT	none	No primary nor secondary outcomes detected	None
14.	SAAW	none	No primary nor secondary outcomes detected	None
15.	SAAB	none	No primary nor secondary outcomes detected	None
16.	SBAX	mortality	1 death on duloxetine	1 death on duloxetine also noted
17.	SBAV	none	No primary nor secondary outcomes detected	None
18.	SBAM	none	No primary nor secondary outcomes detected	None
19.	SAAA	none	No primary nor secondary outcomes detected	No summary report available
20.	SAAH	none	No primary nor secondary outcomes detected	No summary report available
21.	SAAI	none	No primary nor secondary outcomes detected	No summary report available
22.	HMBOa	none	No primary nor secondary outcomes detected	No summary report available
23.	HMAW	mortality	1 death on placebo (2 deaths on duloxetine occurred in the extension phase of this trial, for which we did not have a CSR)	2 deaths on duloxetine and 1 on placebo also noted

Drug: fluoxetine				
Trial No.	**Trial Name**	**Relevant Outcomes**	**From clinical study report (CSRs)**	**From Lilly website online summary reports**
24.	X065	suicidality	2 suicide attempts on fluoxetine	2 suicide attempts on fluoxetine also noted
		aggressive behaviour	1 event on placebo	Missing*
		akathisia	1 event on fluoxetine and 1 on placebo	Missing*
25.	HCJE	suicidality	1 suicide attempt and 1 suicidal ideation on fluoxetine and 1 suicide attempt on placebo	Missing
		aggressive behaviour	5 events on fluoxetine and 5 on placebo	Only 2 events on fluoxetine and 5 on placebo listed
		akathisia	3 events on fluoxetine	Only 2 events on fluoxetine listed
26.	HCJW	suicidality	2 suicide attempts on fluoxetine and 1 on placebo	2 suicide attempts on fluoxetine and 1 on placebo also noted
		aggressive behaviour	1 event on fluoxetine	1 event on fluoxetine also noted
		akathisia	1 event on fluoxetine	1 event on fluoxetine also noted

* The online summary report only had a table of solicited adverse events (from a pre-defined checklist) and not unsolicited adverse events.

6. Additional analyses done using Laughren 2006 FDA report[1], Table 30 and Vanderburg 2009[2] study for sertraline

Data source	No of trials	Active sertraline arm		Placebo arm		Crude Relative Risk [95% confidence intervals (CI)]
		Number of episodes	Number of subjects	Number of episodes	Number of subjects	
FDA data from Table 30 Laughren 2006[1], Suicides, Self harm or suicide attempt	66	7	6950	7	6047	0.87 [0.31, 2.48]
Vanderburg 2009[2] Table 2, short-term studies Suicidality codes 1 and 2 (suicides and suicide attempts)	95	5	6561	8	5480	0.52 [0.17, 1.59]
Vanderburg 2009[2] Table 3, all duration studies Suicidality codes 1 and 2 (suicides and suicide attempts)	Not stated	25	10917	14	9006	1.47 [0.77, 2.83]
Gunnell 2005[3] study data as stated in Table 30 Laughren 2006[1] Suicides and non-fatal self-harm	156	24	7169	8	5108	2.14 [0.96, 4.75]

References:

1. Laughren TP. Overview for December 13 Meeting of Psychopharmacologic Drugs Advisory Committee (PDAC). 2006. Available online from: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-fda.pdf [Accessed 22 October 2013]. (Reference 7 in manuscript).
2. Vanderburg DG, Batzar E, Fogel I, et al. A pooled analysis of suicidality in double-blind, placebo-controlled studies of sertraline in adults. *J Clin Psychiatry* 2009;70:674-83. (Reference 39 in manuscript).
3. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330:385. (Reference 8 in manuscript).

Appendices for research article 2:

Supplementary Data A – Statistical details

Supplementary Data B - Additional results, figures for meta-analyses results for adults

Supplementary Data C – Simulation study

Supplementary Data D – SAS code (data sets and analysis code)

Supplementary Data Document - A: Statistical details

To describe the applied methods in some more mathematical depth we use the following notation: Given are K (i = 1,…, K) independent studies to compare two treatments (1 = treatment or 0 = control). The outcome is binary and takes the values 1 (= Yes) or 0 (= No). Thus, the results from a single study i can be displayed in a 2 x 2 table:

	Outcome: Yes	Outcome: No	
Treatment	n_{11i}	n_{10i}	n_{1+i}
Control	n_{01i}	n_{00i}	n_{0+i}
	n_{+1i}	n_{+0i}	n_{++i}

The observed proportions of outcomes are denoted $p_{1i} = n_{11i}/n_{+1i}$ in the treatment and $p_{0i} = n_{01i}/n_{+1i}$ in the control group.

Yusuf-Peto's Odds Ratio

The pooled log odds ratio from Yusuf-Peto is obtained by considering $O_i = n_{11i}$ (the observed number of outcomes in the treatment group for study i), $E_i = n_{+1i}n_{1+i}/n_{++i}$ (the expected number of events in the treatment group for study i under the null hypothesis of no treatment difference) and $V_i = (n_{+1i}n_{+0i}n_{1+i}n_{0+i})/(n_{++i}n_{++i}(n_{++i}-1))$ by

$$\text{LogOR}_{YP} = \sum_{i=1}^{K}(O_i - E_i) \Big/ \sum_{i=1}^{K} V_i$$

With an estimate of the approximate variance

$$\text{Var}(\text{LogOR}_{YP}) = \sum_{i=1}^{K} V_i$$

we can then compute a standard (1-a)-Wald confidence interval by multiplying the square root of $\text{Var}(\text{LogOR}_{YP})$ with the respective (1-a/2)-quantile of the standard normal distribution and adding and subtracting the resulting term from LogOR_{YP}.

Generalized Linear Mixed Models (GLMM)

In essence, the three estimates given in the subchapters 2.2, 2.3, and 2.4. can be collected under the heading of this model class. To be concrete, we denote π_i as the true outcome probability in study i and write

$$\text{Logit}(\pi_i)=\text{Log}\left[\pi_i/\left(1-\pi_i\right)\right]=a+u_i+bx, \quad (1)$$

with b denoting the treatment effect (as a log odds ratio), x=1 for the treatment and x=0 for the control group. The random effect u_i is assumed to be normally distributed with mean 0 and variance s^2 ($N(0,s^2)$).

This model is a special case of a GLMM and actually constitutes a logistic regression model with a random intercept for the studies and a single fixed effect covariate for treatment. There are numerous possibilities to estimate the parameters a, b, and s^2. In the work reported here we used penalized quasi-likelihood estimation[1] (PQL) to arrive at the GLMM estimate (2.2) and MCMC estimation to arrive at the estimates from the Bayesian approach (2.4). For the Bayesian approach we also have to specify prior distributions for the parameters and we chose non-informative priors which are given in the main text.

In the conditional logistic regression approach (2.3) we use the same model but do no longer assume a normal distribution for the random intercept. We rather use the fact that the conditional likelihood function of the treatment effect b, given the sufficient statistics for the $a+u_i$, in model (1) is equivalent to the likelihood in a stratified (or matched) case-control study[2]. Actually this means conditioning out the study effect from the likelihood function and therefore we do not have to make any assumption about the study effect. As a further consequence, we only get estimates for b, but none for a and s^2.

In the context of meta-analysis we identify the strata with the single studies, the number of outcomes (n_{+1i}) with the cases in the i-th study, and the number of patients without the outcome (n_{+0i}) as the respective controls. As such, each software that can fit stratified case-control studies (e.g., the PHREG procedure in SAS with the STRATA-statement) can be used to estimate the treatment effect via conditional logistic regression. These procedures are asymptotic by definition but it might be interesting to note that the conditioning principle can also be used to derive exact estimates from this model, and we gave SAS code to calculate exact estimates of odds ratios in a previous paper[3].

Beta-binomial model

The beta-binomial model is also a statistical model for logistic regression with correlated responses and it is also a random effect model[4,5]. However, there is no random intercept involved as in model (1). The crucial difference is rather that we assume a random distribution for the outcome probabilities π_{0i} in the control groups from the single studies. To be concrete, these are assumed to be beta-distributed with parameters a and b with $m=a/(a+b)$ being the mean, and $m(1-m)f/(1+f)$ with $f=1/(a+b)$ the variance of this distribution. Interestingly, the correlation of outcomes of two observations from a single study ("intra-study-correlation") can also be derived via $r=1/(a+b+1)$.

To apply the beta-binomial for the meta-analytic situation and thus to link the treatment groups from the single studies to the control groups, we write

$$\text{Logit}(m)=\tilde{a}+\tilde{b}x \qquad (2)$$

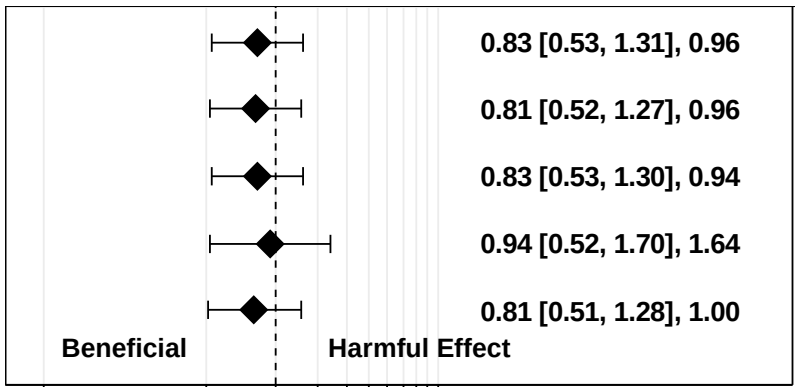
with (similar to (1)) $\tilde{b}$ denoting the treatment effect (as a log-odds ratio), but now from the beta-binomial model, x=1 for the treatment and x=0 for the control group. As the mean mis fixed if we have estimates for a and b, this models also has three parameters that must be estimated. For example, in the accompanying SAS code we estimate r = 1/(a+b+1) together with $\tilde{a}$ and $\tilde{b}$. Very conveniently, these parameters can be collected (as opposed to model (1)) in a closed form likelihood function.

References

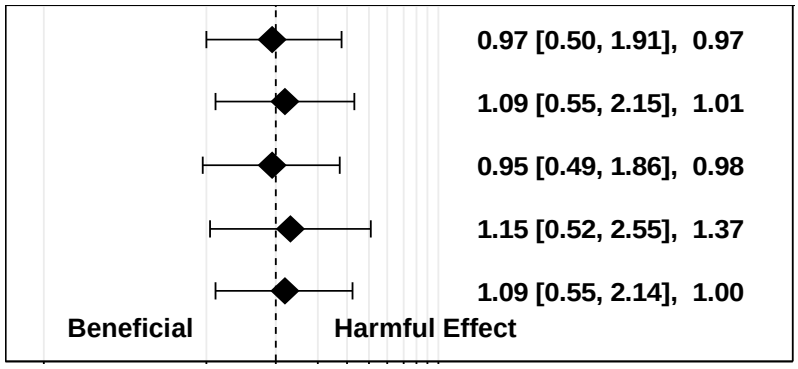
1. Breslow NR, Clayton DG. Approximate inference in generalized linear mixed models. Journal of the American Statistical Association 1993; 88:9-25.
2. Diggle PJ, Liang K-Y, Zeger SL. Analysis of Longitudinal Data. Oxford: Oxford University Press; 1994.
3. Kuss O, Gromann C. An exact test for meta-analysis with binary endpoints. Methods of Information in Medicine 2007; 46(6): 662-8.
4. Agresti A. Categorical Data Analysis. 2nd ed. Hoboken, New Jersey, USA: John Wiley & Sons; 2002.
5. Kuss O. Statistical methods for meta-analyses including information from studies without any events—add nothing to nothing and succeed nevertheless. Statistics in Medicine 2014; 34(7): 1097-116.

Supplementary Data B: Additional results, figures for meta-analyses results for adults

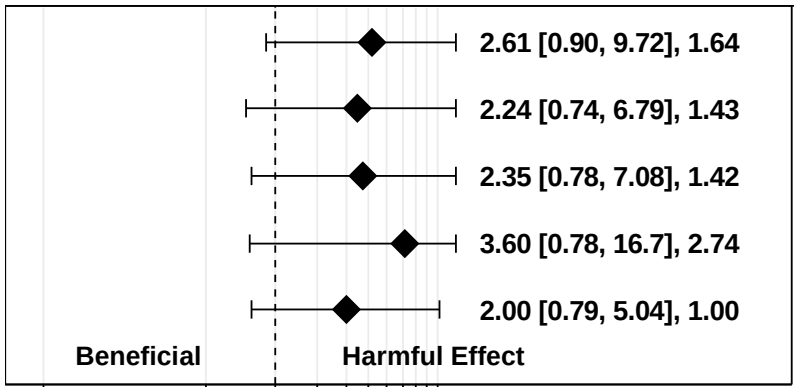
Supplementary Data Figure 1: Comparison of odds ratio estimates using the different methods for suicidality (adults).



Supplementary Data Figure 2: Comparison of odds ratio estimates using the different methods for aggressive behaviour (adults).



Supplementary Data Figure 3: Comparison of odds ratio estimates using the different methods for akathisia (adults).



Supplementary Data Document - C

In this supplementary document we report on a small simulation study that used the SAS code from our previous work (Kuss, 2015), but mimicked the observed data sets for the seven outcomes from the antidepressant trials as closely as possible. To this task, we fixed the number of studies, the event probability in the control group and the treatment effect at the observed values for the seven data sets (Table 1). The sample sizes for the single studies were generated from a log-normal distribution with mean 4.615 and standard deviation of 1.1, a distribution which was informed from a systematic review of 77,237 single studies (Turner, 2012)

As the Yusuf-Peto method is the only estimation method which assumes an underlying fixed effects model, we generated meta-analyses from a true fixed effects model, and also from a true random effects model, both for true odds ratios. The τ^2 for the random effects model were generated, again informed by the Turner (2012) review, from a log-normal distribution with mean -1.47, standard deviation 1.65, and skewness -0.55.

For each of the 14 simulation settings (7 outcomes for a fixed, and a random effects model, respectively) we generated 10.000 meta-analyses and estimated the respective parameters (the log-odds ratio and a 95% confidence interval) from each of the five statistical models under study.

To compare the models we report median bias and empirical coverage, that is, the proportion with which the calculated 95% confidence interval includes the true treatment effect from the simulation. The results are given in Figure 1 and 2 for the fixed effects model and in Figures 3 and 4 for the random effects model.

As the Yusuf-Peto is the only method that assumes a fixed effect model we expect a decent performance of it when the simulation data were generated from the fixed effect model. Indeed, in Figures 1 and 2 the Yusuf-Peto performs well and sometimes even better as compared to the other methods. In comparison to the beta-binomial model the Yusuf-Peto method is, over all 7 scenarios, better in terms of bias and similar in terms of empirical coverage.

It is somewhat surprising that the Yusuf-Peto method also performs not that bad in the random effects situation in Figures 3 and 4. For bias as well as for the empirical coverage it outperforms some of the other methods. In comparison to the beta-binomial model, however, the performance of the Yusuf-Peto method is inferior. It has larger bias, and the average coverage over all 7 scenarios is 0.80 as compared to 0.90 from the beta-binomial model.

Table 1: Fixed values for the number of studies, the event probability in the control group and the treatment effect (odds ratio) in the seven simulation scenarios.

Outcome	Number of studies	Event probability in the control group	Treatment effect (odds ratio)
All-cause mortality, Adults	57	0.0007	1.37
Suicidality, Adults	57	0.0060	0.83
Suicidality, Children	11	0.0107	2.73
Aggressive behaviour, Adults	57	0.0026	0.95
Aggressive behaviour, Children	11	0.0127	3.01
Akathisia, Adults	58	0.0007	2.35
Akathisia, Children	11	0.0020	2.28

Figure 1: Median bias on the log odds scale from 10.000 simulated meta-analyses from a fixed effects model in the seven observed scenarios.
The simulation scenarios on the x-axis are described by the abbreviations “Mort” for all-cause mortality, “Suic” for suicidality, “Aggr” for aggressive behaviour, and “Akat” for Akathisia, “A” and “C” denote the respective scenarios for adults and children. In terms of the statistical models “CLR” denotes the conditional logistic model (2.3), “MCMC” the Bayesian approach (2.4), and “PQL” the GLMM approach (2.2).

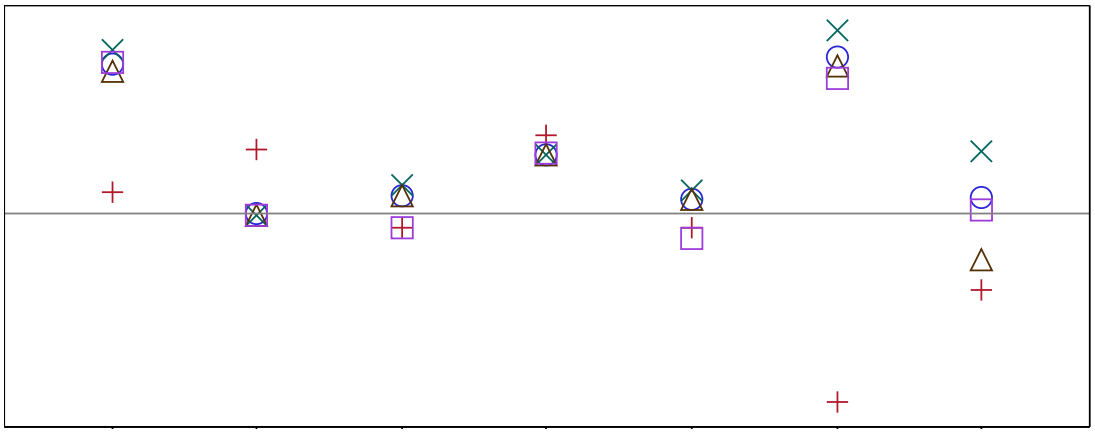


Figure 2: Empirical coverage to the 95% level from 10.000 simulated meta-analyses from a fixed effects model in the seven observed scenarios.
The simulation scenarios on the x-axis are described by the abbreviations “Mort” for all-cause mortality, “Suic” for suicidality, “Aggr” for aggressive behaviour, and “Akat” for Akathisia, “A” and “C” denote the respective scenarios for adults and children. In terms of the statistical models “CLR” denotes the conditional logistic model (2.3), “MCMC” the Bayesian approach (2.4), and “PQL” the GLMM approach (2.2).

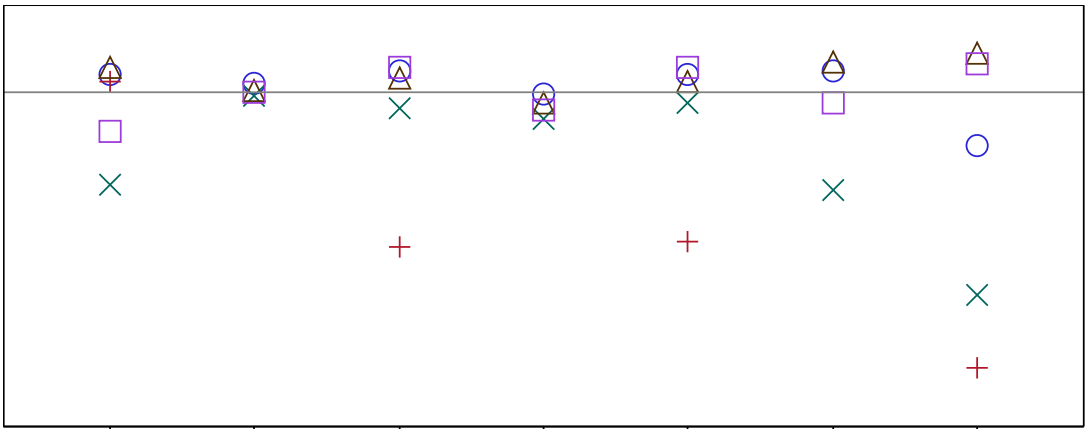


Figure 3: Median bias on the log odds scale from 10.000 simulated meta-analyses from a random effects model in the seven observed scenarios.
The simulation scenarios on the x-axis are described by the abbreviations “Mort” for all-cause mortality, “Suic” for suicidality, “Aggr” for aggressive behaviour, and “Akat” for Akathisia, “A” and “C” denote the respective scenarios for adults and children. In terms of the statistical models “CLR” denotes the conditional logistic model (2.3), “MCMC” the Bayesian approach (2.4), and “PQL” the GLMM approach (2.2).

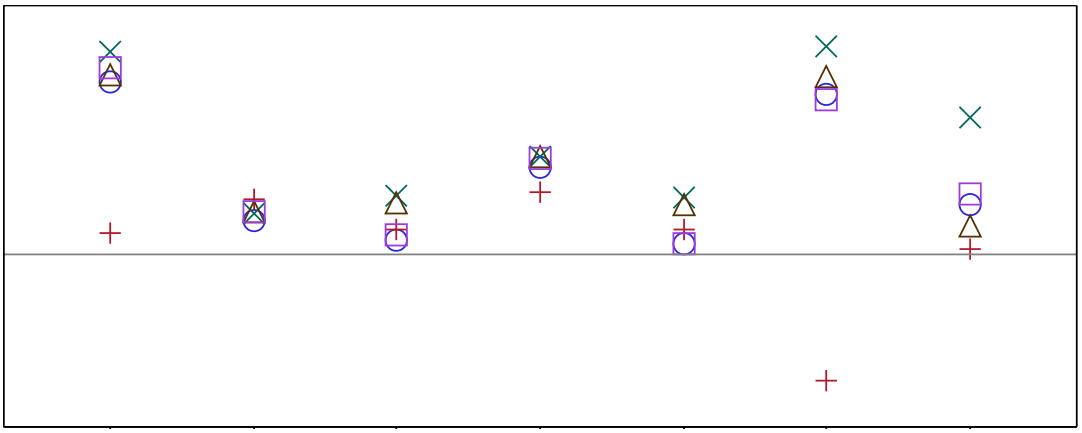
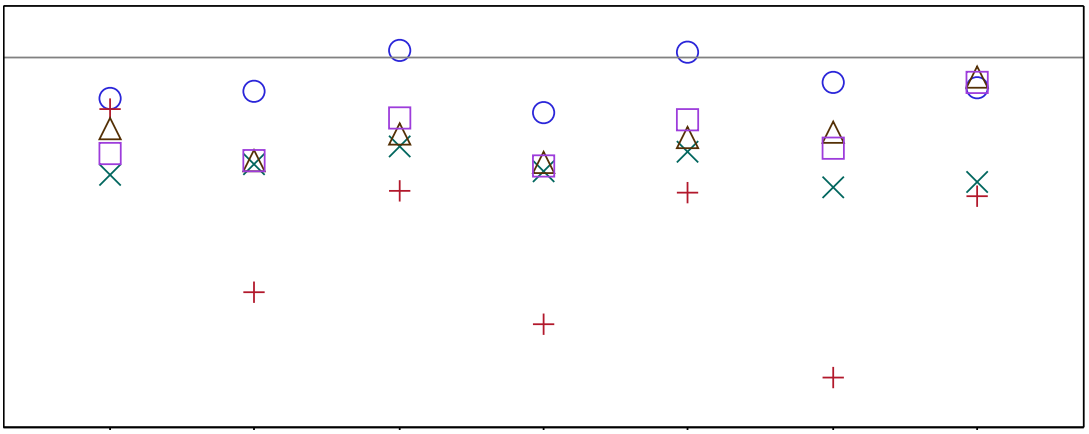


Figure 4: Empirical coverage to the 95% level from 10.000 simulated meta-analyses from a random effects model in the seven observed scenarios.
The simulation scenarios on the x-axis are described by the abbreviations “Mort” for all-cause mortality, “Suic” for suicidality, “Aggr” for aggressive behaviour, and “Akat” for Akathisia, “A” and “C” denote the respective scenarios for adults and children. In terms of the statistical models “CLR” denotes the conditional logistic model (2.3), “MCMC” the Bayesian approach (2.4), and “PQL” the GLMM approach (2.2).



References

Kuss O. Statistical methods for meta-analyses including information from studies without any events-add nothing to nothing and succeed nevertheless. Stat Med. 2015 Mar 30;34(7):1097-116.

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. International Journal of Epidemiology 2012; 41(3):818–827.

Supplementary Data Document D – Data set and SAS code

```
* PAPERCODE.SAS

  SAS data and code to perform the meta-analyses in
  Sharma T, Gøtzsche PC, Kuss O. Meta-analyses of rare binary adverse events data from antidepressant trials:
  determining the validity of estimates across different statistical methods.

  The seven data sets are read in simple DATA steps, and the meta-analysis results are computed with the macro
  %SparseMA.

  Date: 07.04.2017
;

  options pagesize=80 linesize=160 nodate nonumber ;

  proc format;
       value treat 0="Placebo" 1=" Drug ";
       value event 0="No " 1=" Yes";
       value sparse 1="Regular"  2="Single-zero treatment" 3="Single-zero control" 4="Double-zero";
  run;

********** READING DATA SETS
*****************************************************************************************************
**********;

  data AllCauseMortality_Adult;
       input study $13. st nt sc nc;
       TotalNumber=nt+nc;
       index=1;
     * Define Sparseness;
       sparse=1;
       if (st=0 and sc ne 0) then sparse=2;
       if (sc=0 and st ne 0) then sparse=3;
       if st=0 and sc=0 then sparse=4;
       format sparse sparse.;
       cards;
Trial 01          0     103   0     70
Trial 02          0     119   0     75
```

Trial 03	2	188	1	93
Trial 04	0	293	0	99
Trial 05	0	123	0	122
Trial 06	0	128	0	139
Trial 07	0	136	0	142
Trial 08	1	175	0	90
Trial 09	0	264	0	89
Trial 10	0	89	0	88
Trial 11	0	390	0	126
Trial 12	0	53	0	52
Trial 13	0	247	0	247
Trial 14	0	415	0	138
Trial 15	0	221	0	67
Trial 16	1	227	0	231
Trial 17	0	344	0	339
Trial 18	0	55	0	54
Trial 19	0	55	0	37
Trial 20	0	16	0	16
Trial 21	0	47	0	44
Trial 22	0	104	0	103
Trial 23	2	342	1	115
Trial 30	0	160	1	162
Trial 31	1	151	0	156
Trial 32	0	365	0	186
Trial 35	0	96	0	26
Trial 36	0	278	0	91
Trial 37	0	149	0	150
Trial 38	0	151	0	37
Trial 39	0	129	0	129
Trial 40	0	159	0	40
Trial 41	0	43	0	42
Trial 44	0	100	0	108
Trial 45	0	86	0	83
Trial 46	0	94	0	93
Trial 47	0	96	0	97
Trial 48	0	211	0	204
Trial 49	0	135	0	69
Trial 50	0	76	0	78
Trial 51 & 52	0	44	0	43
Trial 53 & 54	0	241	0	84

```
Trial 55          0     86    0     82
Trial 57          0     119   0     38
Trial 58          0     132   0     45
Trial 59          0     85    0     88
Trial 60          0     88    0     90
Trial 61          0     103   0     99
Trial 62          0     181   1     175
Trial 63          0     72    0     76
Trial 64          0     315   0     152
Trial 65          0     266   0     92
Trial 66          0     83    0     82
Trial 67          0     238   0     80
Trial 68          0     100   0     104
Trial 69          1     167   0     83
Trial 70          1     180   0     68
;run;


data AllCauseMort_Children;
     input study $8. st nt sc nc;
     TotalNumber=nt+nc;
     index=1;
   * Define Sparseness;
     sparse=1;
     if (st=0 and sc ne 0) then sparse=2;
     if (sc=0 and st ne 0) then sparse=3;
     if st=0 and sc=0 then sparse=4;
     format sparse sparse.;
     cards;
Trial 24    0     48    0     48
Trial 25    0     109   0     110
Trial 26    0     71    0     32
Trial 27    0     93    0     87
Trial 28    0     187   0     99
Trial 29    0     104   0     102
Trial 33    0     165   0     157
Trial 34    0     100   0     107
Trial 42    0     97    0     91
Trial 43    0     92    0     96
Trial 56    0     94    0     95
```

```
;run;


data Suicidality_Adult;
     input study $13. st nt sc nc;
     TotalNumber=nt+nc;
     index=1;
   * Define Sparseness;
     sparse=1;
     if (st=0 and sc ne 0) then sparse=2;
     if (sc=0 and st ne 0) then sparse=3;
     if st=0 and sc=0 then sparse=4;
     format sparse sparse.;
     cards;
Trial 01          0     103   0     70
Trial 02          0     119   0     75
Trial 03          1     188   1     93
Trial 04          1     196   0     99
Trial 05          3     123   0     122
Trial 06          1     128   3     139
Trial 07          1     136   0     142
Trial 08          2     264   0     90
Trial 09          2     264   0     89
Trial 10          0     89    0     88
Trial 11          7     390   2     126
Trial 12          0     53    0     52
Trial 13          0     247   0     247
Trial 14          0     415   0     138
Trial 15          0     221   0     67
Trial 16          0     227   0     231
Trial 17          0     344   0     339
Trial 18          0     55    0     54
Trial 19          0     55    0     37
Trial 20          0     16    0     16
Trial 21          0     47    0     44
Trial 22          0     104   0     103
Trial 23          0     342   0     115
Trial 30          2     160   4     162
Trial 31          1     151   0     156
Trial 32          3     365   1     186
```

```
Trial 35          0     96    0     26
Trial 36          0     278   0     91
Trial 37          0     149   0     150
Trial 38          2     151   1     37
Trial 39          0     129   2     129
Trial 40          1     159   1     40
Trial 41          0     43    0     42
Trial 44          2     100   3     108
Trial 45          3     86    3     83
Trial 46          1     94    0     93
Trial 47          1     96    0     97
Trial 48          1     211   0     204
Trial 49          0     135   1     69
Trial 50          1     76    0     78
Trial 51 & 52     0     44    1     43
Trial 53 & 54     3     241   0     84
Trial 55          0     86    0     82
Trial 57          0     119   0     38
Trial 58          0     132   0     45
Trial 59          0     85    1     88
Trial 60          0     88    0     90
Trial 61          0     103   0     99
Trial 62          0     181   0     175
Trial 63          0     72    1     76
Trial 64          0     315   1     152
Trial 65          0     266   0     92
Trial 66          0     83    0     82
Trial 67          1     238   1     80
Trial 68          0     100   1     104
Trial 69          8     249   1     83
Trial 70          2     180   6     68
;run;


data Suicidality_Children;
     input study $8. st nt sc nc;
     TotalNumber=nt+nc;
     index=1;
   * Define Sparseness;
     sparse=1;
```

```
     if (st=0 and sc ne 0) then sparse=2;
     if (sc=0 and st ne 0) then sparse=3;
     if st=0 and sc=0 then sparse=4;
     format sparse sparse.;
     cards;
Trial 24    2     48    0     48
Trial 25    2     109   1     110
Trial 26    2     71    1     32
Trial 27    8     93    1     87
Trial 28    8     187   4     99
Trial 29    5     104   1     102
Trial 33    2     165   0     157
Trial 34    1     100   0     107
Trial 42    3     97    0     91
Trial 43    2     92    2     96
Trial 56    0     94    1     95
;run;



data Agress_Behav_Adult;
     input study $13. st nt sc nc;
     TotalNumber=nt+nc;
     index=1;
   * Define Sparseness;
     sparse=1;
     if (st=0 and sc ne 0) then sparse=2;
     if (sc=0 and st ne 0) then sparse=3;
     if st=0 and sc=0 then sparse=4;
     format sparse sparse.;
     cards;
Trial 01          0     103   0     70
Trial 02          0     119   0     75
Trial 03          0     274   0     93
Trial 04          1     196   0     99
Trial 05          1     123   2     122
Trial 06          1     128   3     139
Trial 07          2     136   0     142
Trial 08          0     264   0     90
Trial 09          2     264   0     89
```

Trial 10	0	89	2	88
Trial 11	0	390	1	126
Trial 12	0	53	0	52
Trial 13	0	247	0	247
Trial 14	0	415	0	138
Trial 15	0	221	0	67
Trial 16	1	227	0	231
Trial 17	0	344	0	339
Trial 18	0	55	0	54
Trial 19	0	55	0	37
Trial 20	0	16	0	16
Trial 21	0	47	0	44
Trial 22	0	104	0	103
Trial 23	0	342	0	115
Trial 30	1	160	1	162
Trial 31	1	151	0	156
Trial 32	1	365	1	186
Trial 35	0	96	0	26
Trial 36	0	278	0	91
Trial 37	0	149	0	150
Trial 38	1	151	0	37
Trial 39	0	129	2	129
Trial 40	0	159	0	40
Trial 41	0	43	0	42
Trial 44	1	100	0	108
Trial 45	1	86	0	83
Trial 46	0	94	0	93
Trial 47	0	96	0	97
Trial 48	0	211	0	204
Trial 49	1	135	0	69
Trial 50	0	76	0	78
Trial 51 & 52	0	44	0	43
Trial 53 & 54	1	241	0	84
Trial 55	0	86	0	82
Trial 57	0	119	0	38
Trial 58	1	132	0	45
Trial 59	0	85	0	88
Trial 60	0	88	0	90
Trial 61	0	103	0	99
Trial 62	0	181	0	175

```
Trial 63          1     72    0     76
Trial 64          2     157   0     152
Trial 65          0     266   0     92
Trial 66          0     83    0     82
Trial 67          0     238   1     80
Trial 68          1     100   2     104
Trial 69          0     249   0     83
Trial 70          0     180   0     68
;run;


data Agress_Behav_Children;
     input study $8. st nt sc nc;
     TotalNumber=nt+nc;
     index=1;
   * Define Sparseness;
     sparse=1;
     if (st=0 and sc ne 0) then sparse=2;
     if (sc=0 and st ne 0) then sparse=3;
     if st=0 and sc=0 then sparse=4;
     format sparse sparse.;
     cards;
Trial 24 0  48    1     48
Trial 25 5  109   5     110
Trial 26 1  71    0     32
Trial 27 7  93    0     87
Trial 28 3  187   0     99
Trial 29 2  104   0     102
Trial 33 5  165   2     157
Trial 34 10 100   1     107
Trial 42 3  97    0     91
Trial 43 1  92    1     96
Trial 56 4  94    3     95
;run;


data Akathisia_Adult;
     input study $13. st nt sc nc;
     TotalNumber=nt+nc;
     index=1;
```

```
   * Define Sparseness;
     sparse=1;
     if (st=0 and sc ne 0) then sparse=2;
     if (sc=0 and st ne 0) then sparse=3;
     if st=0 and sc=0 then sparse=4;
     format sparse sparse.;
     cards;
Trial 01          3     103   0     70
Trial 02          0     82    1     75
Trial 03          0     274   0     93
Trial 04          0     293   0     99
Trial 05          1     123   0     122
Trial 06          0     128   0     139
Trial 07          0     136   0     142
Trial 08          1     175   0     90
Trial 09          3     177   0     89
Trial 10          2     89    0     88
Trial 11          4     390   3     126
Trial 12          0     53    0     52
Trial 13          0     247   0     247
Trial 14          0     415   0     138
Trial 15          0     221   0     67
Trial 16          0     227   0     231
Trial 17          0     344   0     339
Trial 18          0     55    0     54
Trial 19          0     55    0     37
Trial 20          0     16    0     16
Trial 21          0     47    0     44
Trial 22          0     104   0     103
Trial 23          0     342   0     115
Trial 30          0     160   0     162
Trial 31          0     151   0     156
Trial 32          0     365   0     186
Trial 35          0     96    0     26
Trial 36          0     278   0     91
Trial 37          0     149   0     150
Trial 38          0     151   0     37
Trial 39          0     129   0     129
Trial 40          0     159   0     40
Trial 41          0     43    0     42
```

```
Trial 44          0     100   0     108
Trial 45          0     86    0     83
Trial 46          0     94    0     93
Trial 47          0     96    0     97
Trial 48          0     211   0     204
Trial 49          1     135   0     69
Trial 49          0     135   0     69
Trial 50          0     76    0     78
Trial 51 & 52     0     44    0     43
Trial 53 & 54     1     241   0     84
Trial 55          0     86    0     82
Trial 57          0     119   0     38
Trial 58          0     132   0     45
Trial 59          0     85    0     88
Trial 60          0     88    0     90
Trial 61          0     103   0     99
Trial 62          0     181   0     175
Trial 63          0     72    0     76
Trial 64          0     315   0     152
Trial 65          0     266   0     92
Trial 66          0     83    0     82
Trial 67          0     238   0     80
Trial 68          0     100   0     104
Trial 69          0     249   0     83
Trial 70          1     180   0     68
;run;

data Akathisia_Children;
     input study $8. st nt sc nc;
     TotalNumber=nt+nc;
     index=1;
   * Define Sparseness;
     sparse=1;
     if (st=0 and sc ne 0) then sparse=2;
     if (sc=0 and st ne 0) then sparse=3;
     if st=0 and sc=0 then sparse=4;
     format sparse sparse.;
     cards;
Trial 24    1     48    1     48
Trial 25    3     109   0     110
```

```
Trial 26    1     71    0     32
Trial 27    0     93    0     87
Trial 28    0     187   0     99
Trial 29    0     104   0     102
Trial 33    0     165   0     157
Trial 34    0     100   0     107
Trial 42    0     97    1     91
Trial 43    0     92    0     96
Trial 56    0     94    0     95
;run;


********** ANALYSIS ********************************************************************************;
  %macro SparseMA(dataset=);

       ********* Prepare data sets in different configurations ***************************************;
       * Data set with one line per study;
         data one&dataset;
              set &dataset;
         run;

       * Data set with two lines per study for all procedures that use the events/trial syntax;
         data help&dataset;
              set &dataset;
              by study;
              do i=1 to 2;
                 output;
              end;
         run;

         data double&dataset;
              set help&dataset;
              int=1;
              if i=1 then do; noutcomes=st;ntrials=nt;treatment=1;control=0;end;
              if i=2 then do; noutcomes=sc;ntrials=nc;treatment=0;control=1;end;
         run;

       * "Exploded" data set with one line for every patient;
         data exploded&dataset;
```

```
      set double&dataset;
      do j=1 to ntrials;
         if j <= noutcomes then outcome=1;
         if j >  noutcomes then outcome=0;
         status=2-outcome;
         output;
      end;
  run;

********* Describe sparseness *********************************************;
  proc freq data=&dataset;
       tables sparse;
       title"&dataset, Description of sparseness";
       format sparse sparse.;
  run;

********* Meta-Analysis ***************************************************************************;
  *** Bayesian approach ***;
  *** The results in the paper were derived with SAS 9.4, and we noted slight deviations when using SAS 9.3***;
      ods select none;
      ods graphics on;
      proc mcmc data=double&dataset seed=456456 nmc=10000 nbi=1000 monitor=(a b sigmasquare) DIC
                stats(PERCENTAGE=(2.5 50 97.5))=all plots=(trace autocorr density);
           parms a -5 b 0.1 sigmasquare 0.1;
           prior a ~ normal(0,var=1000000);
           prior b ~ normal(0,var=1000000);
           prior sigmasquare ~ igamma(0.001, s=0.001);

           random intercept ~ normal(0, var=sigmasquare) subject=study;
           pi = logistic(intercept + a + b*treatment);
           model noutcomes ~ binomial(ntrials,pi);

           ods output  PostSummaries=LogOR_MCMC_temp1(where=(Parameter="b")
                       rename=(P50=LogOR_MCMC_PostMedian Mean=LogOR_MCMC_PostMean))
                       PostIntervals=LogOR_MCMC_temp2(where=(Parameter="b")
                       rename=(CredibleLower=CI95L_EqualTail_LogOR_MCMC CredibleUpper=CI95U_EqualTail_LogOR_MCMC
                               HPDLower=CI95L_HPD_LogOR_MCMC HPDUpper=CI95U_HPD_LogOR_MCMC));
           title"&dataset, OR, GLMM, MCMC";
     run;
     ods graphics off;
```

```
     ods select all;


     data LogOR_MCMC(keep=OR_MCMC_PostMedian OR_MCMC_PostMean CI95L_EqualTail_OR_MCMC CI95U_EqualTail_OR_MCMC
                          CI95L_HPD_OR_MCMC CI95U_HPD_OR_MCMC);
          merge LogOR_MCMC_temp1 LogOR_MCMC_temp2;
          OR_MCMC_PostMedian=exp(LogOR_MCMC_PostMedian);
          OR_MCMC_PostMean=exp(LogOR_MCMC_PostMean);

          CI95L_EqualTail_OR_MCMC=exp(CI95L_EqualTail_LogOR_MCMC);
          CI95U_EqualTail_OR_MCMC=exp(CI95U_EqualTail_LogOR_MCMC);

          CI95L_HPD_OR_MCMC=exp(CI95L_HPD_LogOR_MCMC);
          CI95U_HPD_OR_MCMC=exp(CI95U_HPD_LogOR_MCMC);
    run;
    proc print data=LogOR_MCMC noobs;
          var OR_MCMC_PostMean CI95L_EqualTail_OR_MCMC CI95U_EqualTail_OR_MCMC;
          format OR_MCMC_PostMean CI95L_EqualTail_OR_MCMC CI95U_EqualTail_OR_MCMC 5.3;
    run;

*** Conditional logistic regression ***;
    ods select none;
    proc phreg data=exploded&dataset;
          class treatment / param=ref order=formatted descending;
          model outcome*status(0)=treatment / ties=discrete rl=both;
          strata study;
          format treatment treat.;
          ods output ParameterEstimates=LogOR_CondLogReg(rename=(HazardRatio=OR_CondLogReg
                     HRLowerCL=CI95L_OR_CondLogReg HRUpperCL=CI95U_OR_CondLogReg));
          title"&dataset, OR, PHREG, Conditional logistic regression";
    run;
    ods select all;

    proc print data=LogOR_CondLogReg noobs;
          var OR_CondLogReg CI95L_OR_CondLogReg CI95U_OR_CondLogReg;
          format OR_CondLogReg CI95L_OR_CondLogReg CI95U_OR_CondLogReg 5.3;
    run;

*** Generalised Linear Mixed Model (GLMM) ***;
    ods select none;
```

```
    proc glimmix data=double&dataset order=formatted;
         class treatment study;
         model noutcomes/ntrials=treatment / d=bin link=logit solution cl ddf=10000;
         random intercept / subject=study;
         estimate "treatment" treatment 1 -1 / cl exp;
         ods output Estimates=LogOR_PQL(rename=(Estimate=LogOR_PQL Lower=CI95L_LogOR_PQL
                                                Upper=CI95U_LogOR_PQL ExpEstimate=OR_PQL ExpLower=CI95L_OR_PQL
                                                ExpUpper=CI95U_OR_PQL));

         title"&dataset, GLMM, PQL, PROC GLIMMIX";
         format treatment treat.;
    run;
    ods select all;
    proc print data=LogOR_PQL noobs;
         var OR_PQL CI95L_OR_PQL CI95U_OR_PQL;
         format OR_PQL CI95L_OR_PQL CI95U_OR_PQL 5.3;
    run;

*** Beta-binomial model ***;
    ods select none;
    proc nlmixed data=double&dataset df=10000;
       * Give starting values for the model parameters;
         parms rho=0.1 atilde=-5 btilde=-0.1;

       * Define LogLikelihood function;
         mu= exp(atilde + btilde*treatment)/ (1 + exp(atilde + btilde*treatment));

       * ALPHA and BETA are the parameters of the underlying beta distribution;
         alpha=mu*(1-rho)/rho;
         beta=(1-mu)*(1-rho)/rho;

         ll= lgamma(ntrials+1)+lgamma(noutcomes+alpha)+lgamma(ntrials-noutcomes+beta)+lgamma(alpha+beta)
            -lgamma(noutcomes+1)-lgamma(ntrials-noutcomes+1)-lgamma(ntrials+alpha+beta)-lgamma(alpha)
            -lgamma(beta);

         model noutcomes ~ general(ll);

       * Additional Estimates;
         estimate "LogOR" btilde;
```

```
     ods output AdditionalEstimates=LogOR_BBIN_temp(where=(Label="LogOR") rename=(Estimate=LogOR_BBIN
                                                    StandardError=SE_LogOR_BBIN));
     title"&dataset, OR, Beta-binomial model, NLMIXED";

run;
ods select all;

data OR_BBIN(keep=OR_BBIN CI95L_OR_BBIN CI95U_OR_BBIN SE_LogOR_BBIN);
     set LogOR_BBIN_temp;
     CI95L_LogOR_BBIN =  LogOR_BBIN - probit(0.975)* SE_LogOR_BBIN;
     CI95U_LogOR_BBIN =  LogOR_BBIN + probit(0.975)* SE_LogOR_BBIN;

     OR_BBIN=exp(LogOR_BBIN);
     CI95L_OR_BBIN=exp(CI95L_LogOR_BBIN);
     CI95U_OR_BBIN=exp(CI95U_LogOR_BBIN);
run;
proc print data=OR_BBIN noobs;
     var OR_BBIN CI95L_OR_BBIN CI95U_OR_BBIN;
     format OR_BBIN CI95L_OR_BBIN CI95U_OR_BBIN 5.3;
run;


*** Yusuf-Peto method ***;
data yusufpeto(keep=YPLO SE_YPLO CI95L_YPLO CI95U_YPLO YP_OR CI95L_OR_YP CI95U_OR_YP);
     set &dataset end=lastrecord;

   * Define Parameters to match those from the accompanying technical supplement;
     n11i=St; n01i=Sc;n1pi=Nt;n0pi=Nc;
     np1i=St+Sc;np0i=(Nt-St)+(Nc-Sc);
     nppi=Nt+Nc;

     O_i=n11i;
     E_i=n1pi*np1i/nppi;
     V_i=(np1i*np0i*n1pi*n0pi)/(nppi**2*(nppi-1));

   * Initialize terms that are summarized;
     retain sum_YP_den sum_YP_num 0;

   * Calculate terms that are summed across studies;
     YP_num  = O_i-E_i;
```

```
            YP_den  = V_i;

         * Sum those up;
           sum_YP_den=sum(sum_YP_den+YP_den);
           sum_YP_num=sum(sum_YP_num+YP_num);

         * Calculate estimates and confidence intervals;
           if lastrecord then do;
              YPLO = sum_YP_num/sum_YP_den;
              CI95L_YPLO = YPLO-(probit(0.975)/sqrt(sum_YP_den));
              CI95U_YPLO = YPLO+(probit(0.975)/sqrt(sum_YP_den));
              SE_YPLO = 1/sqrt(sum_YP_den);
              YP_OR = exp(YPLO);
              CI95L_OR_YP = exp(CI95L_YPLO);
              CI95U_OR_YP = exp(CI95U_YPLO);
              output;
           end;
           title"&dataset, Yusuf-Peto";
      run;

      proc print data=yusufpeto noobs;
           var YP_OR CI95L_OR_YP CI95U_OR_YP;
           format YP_OR CI95L_OR_YP CI95U_OR_YP 5.3;
      run;


%mend SparseMA;

options nomlogic nomprint;

%SparseMA(dataset=AllCauseMortality_Adult);
%SparseMA(dataset=Suicidality_Adult);
%SparseMA(dataset=Suicidality_Children);
%SparseMA(dataset=Agress_Behav_Adult);
%SparseMA(dataset=Agress_Behav_Children);
%SparseMA(dataset=Akathisia_Adult);
%SparseMA(dataset=Akathisia_Children);
```

Appendices for research article 3:

Supplementary Document A - Glossary of terms and additional details on methods

Supplementary Document B - Sensitivity analyses using beta-binomial method for secondary outcomes

Supplementary Document C - Funnel plots for the primary and secondary outcomes

Supplementary Document A: Glossary of terms and additional details on methods

Table 1: Glossary of terms from clinical study reports[1-3]

Term	Explanation
Clinical study reports (CSRs)	Clinical study reports (CSRs) are detailed summaries of trial results prepared by the drug industry for submissions to regulatory authorities in order to obtain marketing authorization. They can be of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.
Disposition of patients	There needs to be clear accounting of all patients who entered the study, using figures or tables in the text within the CSR. The numbers of patients who were randomised, and who entered and completed each phase of the study, (or each week/month of the study) should be provided, as well as the reasons for all post-randomisation discontinuations, grouped by treatment and by major reason (lost to follow-up, adverse event, poor compliance etc.).
Adverse events	An adverse event is any undesirable experience associated with the use of a medical product in a patient, which does not necessarily have a causal relationship with this treatment.
Serious adverse event	A serious adverse event as defined by The ICH Guideline on Clinical Safety Data Management, Definitions and Standards for Expedited Reporting is a "any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect."
Adverse event tables	All adverse events occurring after initiation of study treatments are required to be displayed in summary tables. In most cases, it will also be useful to identify in such tables "treatment emergent signs and symptoms" (TESS; those not seen at baseline and those that worsened even if present at baseline). The tables should list each adverse event, the number of patients in each treatment group in whom the event occurred, and the rate of occurrence. Adverse events should be grouped by body system. Each event may then be divided into defined severity categories (e.g., mild, moderate, severe) if these were used. The tables may also divide the adverse events into those considered at least possibly related to drug use and those considered not related, or use some other causality scheme (e.g., unrelated or possibly, probably, or definitely related).
Patient narratives	Patient narratives are brief summaries required by regulatory authorities for certain events such as any deaths, other serious adverse events and other significant events that are of clinical importance (often events that lead to study discontinuation or changes in dose of study medication).
Individual patient listings (IPL)	Individual patient listings (IPL) are lists containing details of events such as patient identifier, the adverse event (preferred term and reported term), duration of the adverse event, severity (for example, mild, moderate, severe), seriousness (serious/non-serious), action taken (none, dose reduced, treatment stopped, etc), and outcome. IPL are also recommended by the authorities for events similar to those for patient narratives, however additionally such lists for all adverse events for all patients are also available (often upon request), and are often placed within appendices.
Appendices	This section is usually at the end of every CSR and should be prefaced by a full list of all appendices available for the study report. The appendices usually should contain the following: protocol and protocol

Term	Explanation
	amendments, sample case report form (unique pages only), list of ethics committees, representative written information for patient and sample consent forms, list and description of investigators and other important participants in the study, signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, listing of patients receiving test drug, randomisation scheme and codes, audit certificates (if available), documentation of statistical and inter-laboratory standardisation methods, publications based on the study and those referenced in the report, patient listings for efficacy outcomes, adverse events (individual patient listings required), discontinuations, protocol deviations, laboratory measurements, other individual patient listings, case report forms (CRFs) for deaths, other serious adverse events and events leading to withdrawals (required) and any other CRFs submitted.
Case report forms (CRFs)	Case report forms (CRFs) are paper or electronic questionnaires specifically used in clinical trial research to collect data from each participating site, by the sponsor of the clinical trial. All the collected data on each patient participating in the trial are therefore contained and/or documented within the CRF, including individual data on adverse events.

Additional information on methods

The clinical study reports (CSRs) were obtained from the regulatory agencies through the freedom of information request route. We requested the European Medicines Agency (EMA) for all their CSRs for all trials they had for paroxetine, fluoxetine, sertraline, citalopram, escitalopram, mirtazapine, venlafaxine, and duloxetine, from their archives. We were then informed that they did not have any documents for fluoxetine and those were available from the UK's Medicines and Healthcare products Regulatory Agency (MHRA), so we requested the CSRs for fluoxetine from them. However, we could not get access to CSRs for all trials for all the commonly prescribed drugs we had requested. We also did not receive any case report forms (CRFs) for any of the trials.

We received in total 198 CSRs but these included a number of open-label studies, healthy volunteer studies and cross-over studies. We only included double-blind placebo controlled trials and then further excluded CSRs of trials where we had no information on study drop-out rates.

The CSRs were first obtained as scanned PDF documents, but once converted to a readable format using the 'optical character recognition (OCR)' function of Adobe Acrobat XI Professional they could be searched electronically. Our previous study showed that we could not have the second data extraction done blindly, with the treatment groups masked, as the format and the language used within the CSRs made blinding impossible.

For the trials where there were more than one intervention arm of either an SSRI or SNRI, we combined their data in order to get a single combined SSRI or SNRI drug arm. We also did this for trials where there were different arms of the same drug but of different dosages. We considered all events that occurred post-randomisation including the lead-out phase (where this information was available) but did not include events if there was an extension phase.

The trials had often analysed the data using a modified intention-to-treat (ITT) model where the study participants who had no data recorded (for benefits or harms) post-randomisation and receiving the double-blinded medication were not counted in the calculations. We have included these "no show" patients as they were referred to within the reports in our dataset using the ITT method, as they should have been classified as 'lost to follow-up'. The modified ITT numbers were then used in subsequent tables and figures, so if the text regarding the disposition of patients was not read in its entirety, one would have incorrect values.

References:

(1) Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervolgyi V, Kohlepp P et al. Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. *PLoS Med* 2013; 10(10):e1001526.

(2) Maund E, Tendal B, Hróbjartsson A, Jørgensen KJ, Lundh A, Schroll J et al. Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications. *BMJ* 2014; 348:g3555.

(3) Structure and content of clinical study reports: E3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1995. Available from www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf [Accessed 10 August 2015].

Supplementary Document B: Additional tables and figures and Sensitivity analyses using beta-binomial method for secondary outcomes

Table 1: The main characteristics for the selected trials

Trial number	Trial protocol	Drug	Age (years)	Condition	Dose	Active comparator	Number in placebo arm	Number of SSRI/SNRI (all arms)	Number of other active comparator
D-1	HMAG	duloxetine	18 to 72	MDD with short REM latency	20 mg per day	None	52	53	
D-2	HMAH	duloxetine	18 to 72	MDD	20 or 30 mg per day	None	88	89	
D-3	HMAI	duloxetine	at least 18	MDD	5, 10 or 20 mg per day	clomipramine 150mg/ day	126	390	132
D-4	HMAQa	duloxetine	18 to 65	MDD	20 to 60 mg per day	fluoxetine 20mg/ day	70	103 (70+33)	
D-5	HMAQb	duloxetine	18 to 65	MDD	20 to 60 mg per day	fluoxetine 20mg/ day	75	119 (82+37)	
D-6	HMATa	duloxetine	at least 18	MDD	20 or 40 mg per day	paroxetine 20mg/ day	90	264 (175+89)	
D-7	HMATb	duloxetine	at least 18	MDD	20 or 40 mg per day	paroxetine 20mg/ day	89	264 (177+87)	
D-8	HMAW	duloxetine	at least 18	DPNP	60mg BD, 60mg QD and 20mg QD*	None	115	342	
D-9	HMAYa	duloxetine	at least 18	MDD	20 or 40 mg per day	paroxetine 20mg/ day	93	274 (188+86)	
D-10	HMAYb	duloxetine	at least 18	MDD	20 or 40 mg per day	paroxetine 20mg/ day	99	293 (196+97)	
D-11	HMBC	duloxetine	at least 18	MDD	60 mg per day	None	142	136	
D-12	HMBHa	duloxetine	at least 18	MDD	60 mg per day	None	122	123	
D-13	HMBHb	duloxetine	at least 18	MDD	60 mg per day	None	139	128	
D-14	HMBOa	duloxetine	at least 18	Fibromyalgia with or without MDD	60 mg per day	None	103	104	
D-15	SBAM	duloxetine	18 to 75	SUI in Women electing surgery for severe pure GSI	80 to 120 mg per day	None	54	55	
D-16	SBAT	duloxetine	at least 18	SUI in Women	80 mg per day	None	247	247	
D-17	SBAV	duloxetine	at least 18	SUI or mixed in Women	80 mg per day	None	339	344	

Trial number	Trial protocol	Drug	Age (years)	Condition	Dose	Active comparator	Number in placebo arm	Number of SSRI/SNRI (all arms)	Number of other active comparator
D-18	SBAX	duloxetine	at least 18	SUI or mixed in Women	80 mg per day	None	231	227	
D-19	SAAA	duloxetine	30 to 80	SUI, urge, or mixed	20 mg per day	None	37	55	
D-20	SAAB	duloxetine	18 to 80	SUI or mixed in Women	20mg, 30mg and 40mg per day	None	67	221	
D-21	SAAH	duloxetine	18 to 85	SUI with urinary urgency and PDO	30 or 40 mg per day	None	16	16	
D-22	SAAI	duloxetine	40 to 85	BPH in Men	30 or 40 mg per day	None	44	47	
D-23	SAAW	duloxetine	18 to 65	SUI in Women	20, 40, or 80 mg per day	None	138	415	
F-1	B1Y-MC-HCJE	fluoxetine	8 to <18	MDD	20 to 60 mg per day	None	110	109	
F-2	B1Y-MC-HCJW	fluoxetine	7 to <18	OCD	20 to 60 mg per day	None	32	71	
F-3	B1Y-MC-X065	fluoxetine	8 to <18	MDD	20mg per day**	None	48	48	
P-1	Protocol 595	paroxetine	at least 18	SP	20 to 50 mg per day	None	161	162	
P-2	Protocol 627	paroxetine	at least 18	PTSD	20 to 50 mg per day	None	162	160	
P-3	Protocol 648	paroxetine	at least 18	PTSD	20 to 50 mg per day	None	156	151	
P-4	Protocol 651	paroxetine	at least 18	PTSD	20 or 40 mg per day	None	186	365	
P-5	Protocol 646	paroxetine	at least 18	GAD	20 to 50 mg per day	None	288	278	
P-6	Protocol 329	paroxetine	12 to18	MDD	20 to 40 mg per day	impramine 50 to 300 mg/day	87	93	95
P-7	Protocol 377	paroxetine	13 to18	MDD	20 to 40 mg per day	None	99	187	
P-8	Protocol 676	paroxetine	8 to 17	SAD/ SP	10 to 50 mg per day	None	157	165	
P-9	Protocol 701	paroxetine	7 to 17	MDD	10 to 50 mg per day	None	102	104	

Trial number	Trial protocol	Drug	Age (years)	Condition	Dose	Active comparator	Number in placebo arm	Number of SSRI/SNRI (all arms)	Number of other active comparator
P-10	Protocol 704	paroxetine	7 to 17	OCD	10 to 50 mg per day	None	107	100	
S-1	R-050-101	sertraline	18 to 65	MDD in hospitals	50,100, 200 or 400 mg per day	None	26	96	
S-2	R-050-103	sertraline	18 to 65	MDD	50, 100 or 200 mg per day	None	91	278	
S-3	R-050-104	sertraline	18 to 65	MDD	50, 100 or 200 mg per day	amitriptyline 50, 100, or 150 mg/day	150	149	149
S-4	R-050-113	sertraline	18 to 70	NIDDM	50 to 200 mg per day	None	175	181	
S-5	R-050-310	sertraline	18 to 65	MDD	50, 100, 200 or 400 mg per day	None	37	151	
S-6	R-050-334	sertraline	18 to 70	MDD or bipolar depression	50 to 200 mg per day	None	129	129	
S-7	R-050-336	sertraline	16 to 75	OCD	50 to 200 mg per day	None	78	76	
S-8	R-0601	sertraline	at least 18	GSP	25 to 200 mg per day		204	211	
S-9 and S-10	R-80ce21-0237 and R-86ce21-0248	sertraline	at least 18	OCD	50 to 200 mg per day	None	43	44	
S-11	R-86CE21-0238	sertraline	18 to 60	MDD	50, 100, 200 or 400 mg per day	None	40	159	
S-12	R-86CE21-0247	sertraline	60 and above	MDD	50 to 200 mg per day	desipramine 25 to 150mg/day	42	43	45
S-13 and S-14	R-88CE21-0371 and R-88CE21-0372	sertraline	at least 18	OCD	50, 100 or 200 mg per day	None	84	241	
S-15	R-90ce21-0495	sertraline	at least 18	OCD	25 to 200 mg per day	clomipramine 25 to 250mg/ day	88	87	85

Trial number	Trial protocol	Drug	Age (years)	Condition	Dose	Active comparator	Number in placebo arm	Number of SSRI/SNRI (all arms)	Number of other active comparator
S-16	R-90CE21-0514	sertraline	at least 18	PD	50, 100 or 200 mg per day	None	38	119	
S-17	R-90CE21-0529	sertraline	at least 18	PD	50, 100 or 200 mg per day	None	45	132	
S-18	R-91CE21-0546	sertraline	at least 18	OCD	50 to 200 mg per day	None	82	86	
S-19	R-93CE2 l-0630	sertraline	at least 18	PD	25 to 200 mg per day	None	90	88	
S-20	R-93CE21-0629	sertraline	at least 18	PD	25 to 200 mg per day	None	88	85	
S-21	R-93ce21-0640	sertraline	at least 18	PTSD	25 to 200 mg per day	None	108	100	
S-22	R-93CE21-0641	sertraline	at least 18	PTSD	25 to 200 mg per day	None	83	86	
S-23	R-93CE21-0646	sertraline	at least 18	PD	25 to 100 mg per day	None	99	103	
S-24	R-95CE21-0671	sertraline	at least 18	PTSD	25 to 200 mg per day	None	93	94	
S-25	R-96ce21-0682	sertraline	at least 18	PTSD	25 to 200 mg per day	None	97	96	
S-26	STL-NY-94-004	sertraline	18 to 60	SP	50 to 200 mg per day	None	69	135	
S-27	A0501001	sertraline	6 to 17	MDD	25 to 200 mg per day	None	91	97	
S-28	A0501017	sertraline	6 to 17	MDD	25 to 200 mg per day	None	96	92	
S-29	R-90CE21-0498	sertraline	6 to 17	OCD	25, 50 or 200 mg per day	None	95	94	
V-1	0600A1-372-US	venlafaxine	at least 18	MDD	200, 300 or 375 mg per day	fluoxetine 40, 60 or 80mg/ day	152	315 (157+158)	
V-2	0600A-203-US	venlafaxine	18 to 65	MDD	25, 75, or 125 mg per day	None	92	266	
V-3	0600A-302-US, CA/302	venlafaxine	at least 18	MDD	75 to 200 mg per day	trazodone 150 to 400 mg/ day	76	72	77
V-4	0600A-303-	venlafaxine	at least 18	MDD	75 to 225 mg	imipramine	82	83	82

Trial number	Trial protocol	Drug	Age (years)	Condition	Dose	Active comparator	Number in placebo arm	Number of SSRI/SNRI (all arms)	Number of other active comparator
	US				per day	75 to 225 mg/day			
V-5	0600A-313-US	venlafaxine	18 to 65	MDD	25, 75 or 200 mg per day	None	80	238	
V-6	0600B1-384-US/EU/CA	venlafaxine	at least 18	MDD	150 to 375 mg per day	imipramine 50 to 200mg/day	68	180	187
V-7	0600B-209-US	venlafaxine	at least 18	MDD	75 to 225 mg per day	None	104	100	
V-8	0600B-367-EU	venlafaxine	at least 18	MDD	75 or 150 mg per day	paroxetine 20mg/ day	83	249 (167+82)	

BPH: irritative symptoms of benign prostatic hyperplasia; DPNP: diabetic peripheral neuropathic pain; GAD: generalized anxiety disorder; GSI: genuine stress incontinence; GSP: generalized social phobia; MDD: major depressive disorder; NIDDM: patients with non-insulin-dependent diabetes mellitus for obesity; OCD: obsessive compulsive disorder; PD: panic disorder; PDO: proven detrusor overactivity; PTSD: posttraumatic stress disorder; REM: short rapid eye movement ; SAD: social anxiety disorder; SP: social phobia; SUI: stress urinary incontinence.

* QD (quaque die): once a day and BD: twice a day for trial D-8

**patients unable to tolerate fluoxetine could dose every other day instead of daily dosing for trial F-3

Figure 1a: Sensitivity analyses of overall study drop-out rates on drugs (SSRI or SNRI) versus placebo after exclusion of three trials with a prior single-blind phase of drug

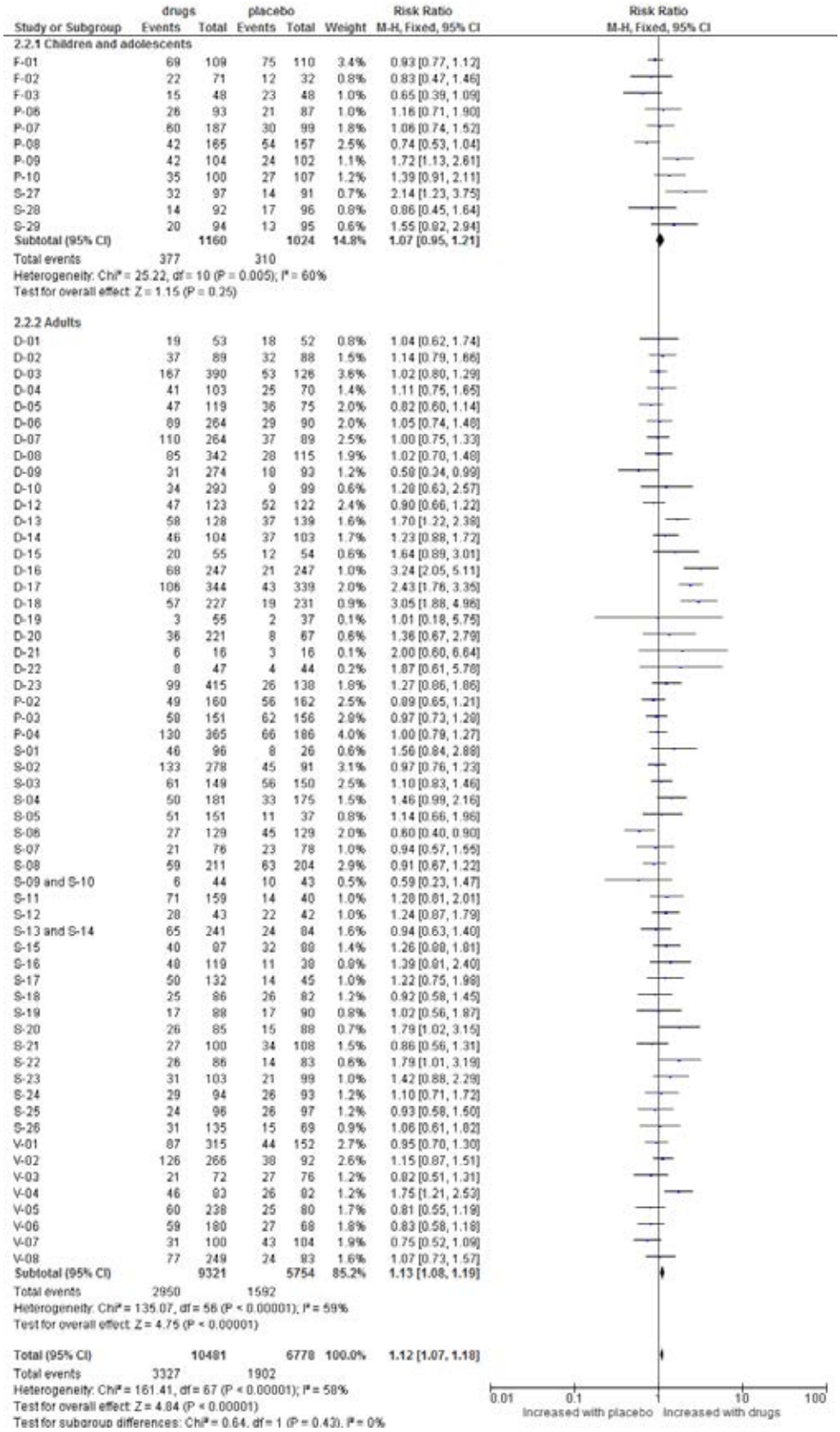


Figure 1b: Sensitivity analyses of overall study drop-out rates on drugs (SSRI or SNRI) versus placebo after exclusion of three trials with fraudulent data or issues with data validity

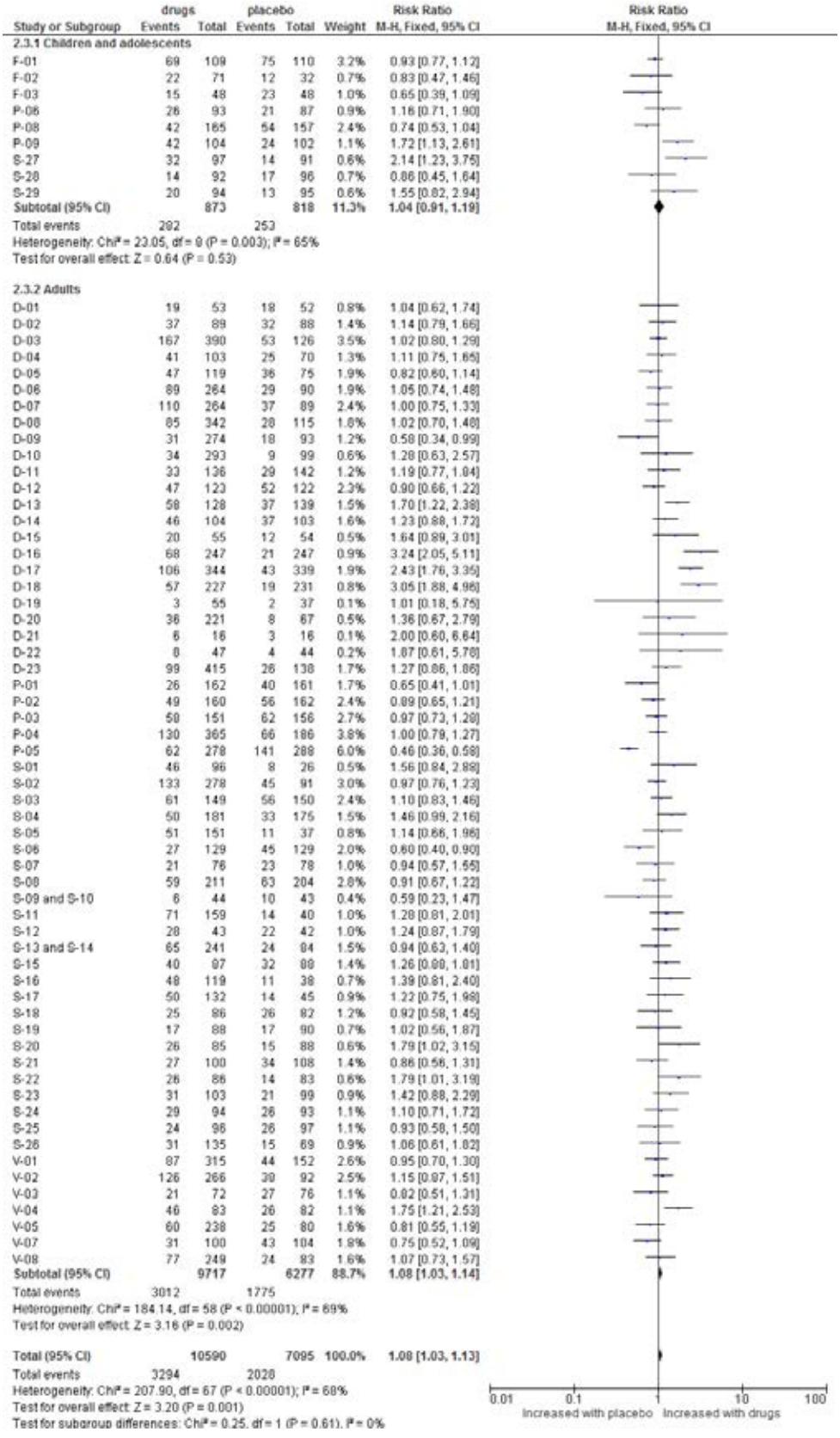


Figure 2: Sensitivity analyses of study discontinuations due to adverse events using Peto's odds ratio post-randomisation

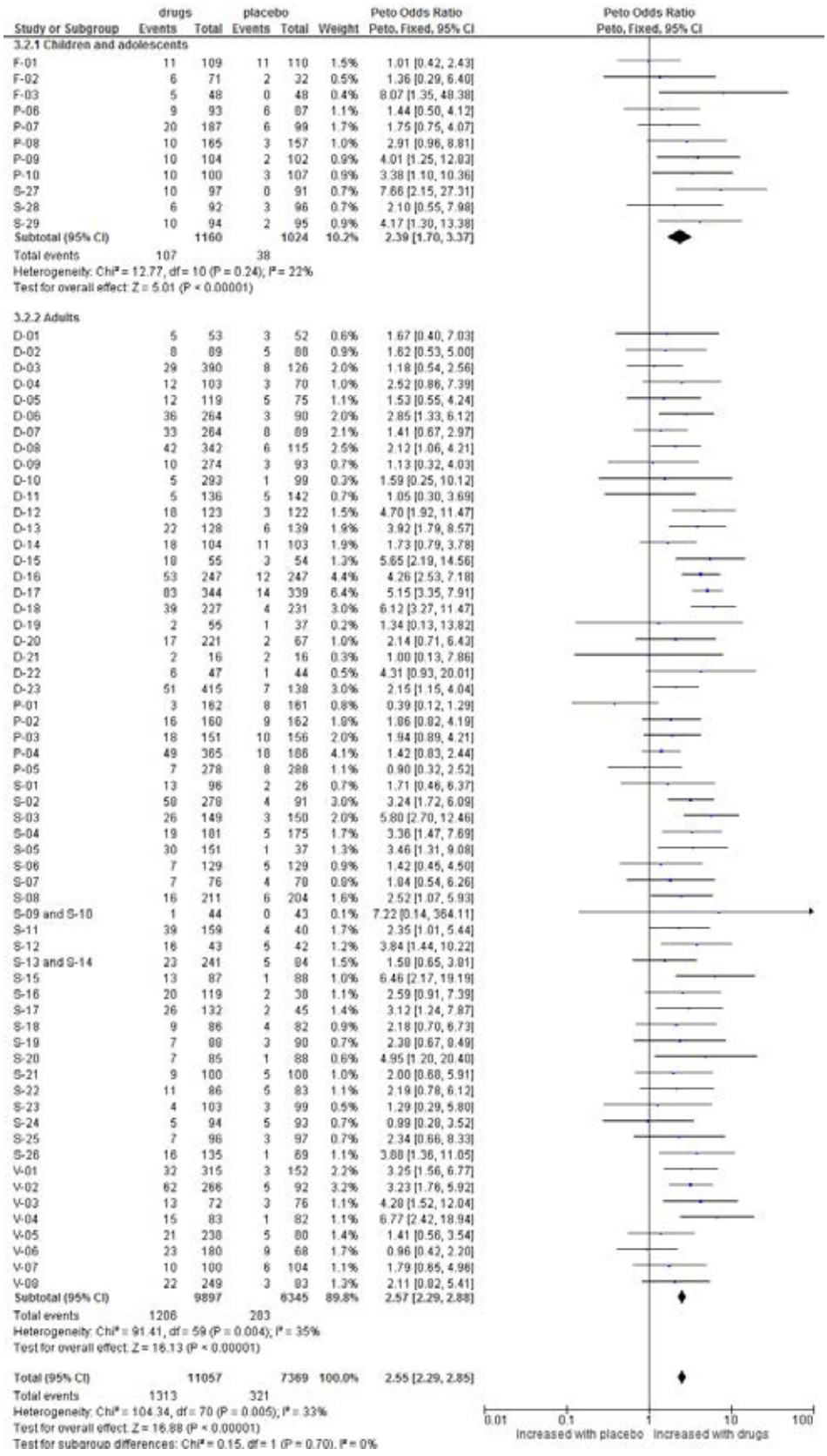
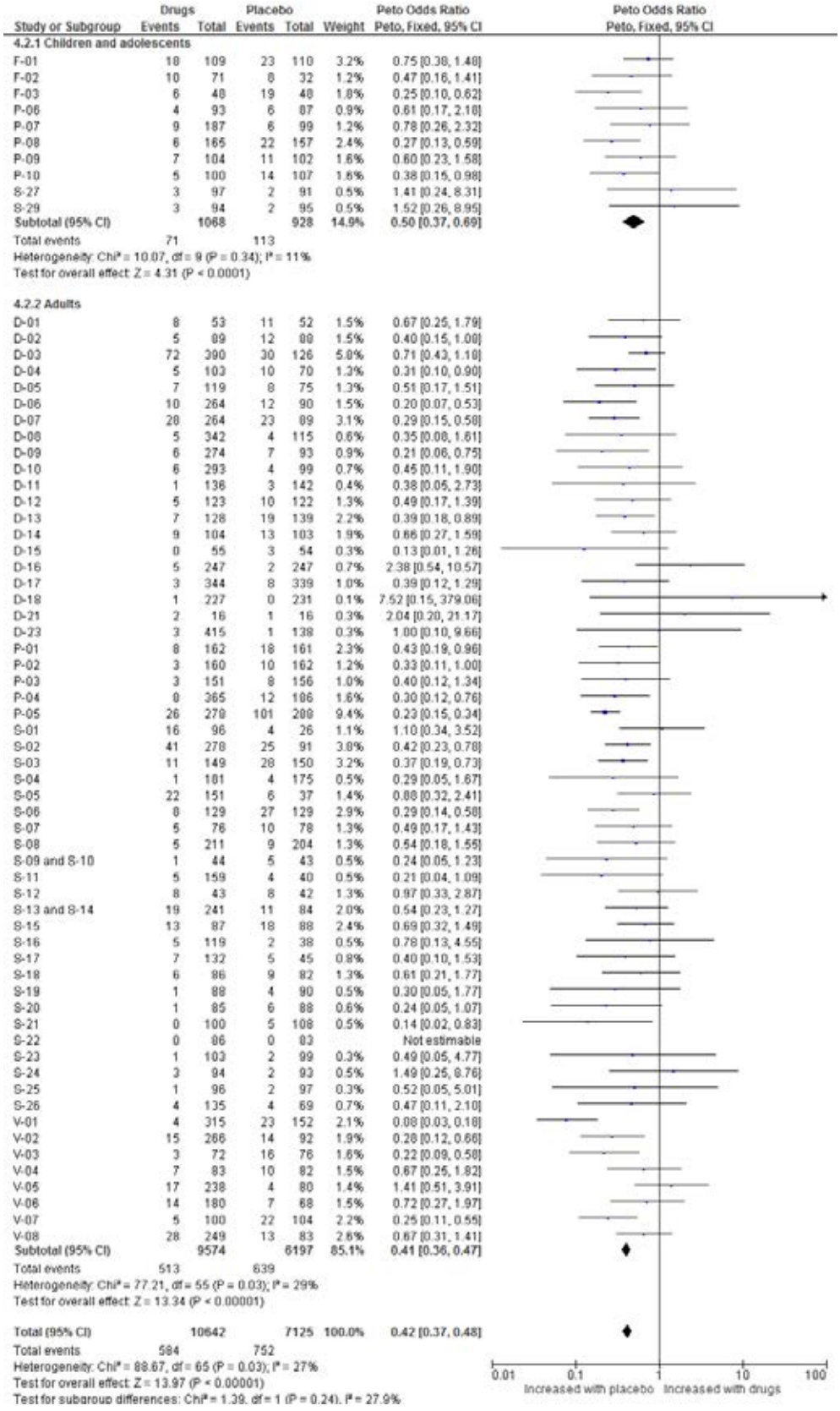


Figure 3: Sensitivity analyses of study drop-out rates due to lack of effect using Peto's odds ratio post-randomisation



Section 2: Sensitivity analyses using beta-binomial method for secondary outcomes

Trials

Trial number	Trial No
D-1	Trial 1
D-2	Trial 2
D-3	Trial 3
D-4	Trial 4
D-5	Trial 5
D-6	Trial 6
D-7	Trial 7
D-8	Trial 8
D-9	Trial 9
D-10	Trial 10
D-11	Trial 11
D-12	Trial 12
D-13	Trial 13
D-14	Trial 14
D-15	Trial 15
D-16	Trial 16
D-17	Trial 17
D-18	Trial 18
D-19	Trial 19
D-20	Trial 20
D-21	Trial 21
D-22	Trial 22
D-23	Trial 23
F-1	Trial 24
F-2	Trial 25
F-3	Trial 26
P-1	Trial 27
P-2	Trial 28
P-3	Trial 29
P-4	Trial 30
P-5	Trial 31
P-6	Trial 32
P-7	Trial 33
P-8	Trial 34
P-9	Trial 35
P-10	Trial 36
S-1	Trial 37

Trial number	Trial No
S-2	Trial 38
S-3	Trial 39
S-4	Trial 40
S-5	Trial 41
S-6	Trial 42
S-7	Trial 43
S-8	Trial 44
S-9 and S-10	Trial 45 & 46
S-11	Trial 47
S-12	Trial 48
S-13 and S-14	Trial 49 & 50
S-15	Trial 51
S-16	Trial 52
S-17	Trial 53
S-18	Trial 54
S-19	Trial 55
S-20	Trial 56
S-21	Trial 57
S-22	Trial 58
S-23	Trial 59
S-24	Trial 60
S-25	Trial 61
S-26	Trial 62
S-27	Trial 63
S-28	Trial 64
S-29	Trial 65
V-1	Trial 66
V-2	Trial 67
V-3	Trial 68
V-4	Trial 69
V-5	Trial 70
V-6	Trial 71
V-7	Trial 72
V-8	Trial 73

A: Discontinuations due to adverse events (tolerability)

SAS code, dataset and results

```
options pagesize=80 linesize=160 nodate nonumber ;
```

```
  proc format;
       value treat 0="Placebo" 1=" Drug ";
       value event 0="No " 1=" Yes";
       value sparse 1="Regular"  2="Single-zero treatment" 3="Single-zero
control" 4="Double-zero";
  run;

********** READING DATA SETS
*******************************************************************************
*********************************************;

data AED;
     input study $13. st nt sc nc;
     TotalNumber=nt+nc;
     index=1;
   * Define Sparseness;
     sparse=1;
     if (st=0 and sc ne 0) then sparse=2;
     if (sc=0 and st ne 0) then sparse=3;
     if st=0 and sc=0 then sparse=4;
     format sparse sparse.;
     cards;

Trial 01              5          53         3          52
Trial 02              8          89         5          88
Trial 03              29         390        8          126
Trial 04              12         103        3          70
Trial 05              41         119        5          75
Trial 06              36         264        3          90
Trial 07              33         264        8          89
Trial 08              42         342        6          115
Trial 09              10         274        3          93
Trial 10              5          293        1          99
Trial 11              5          136        5          142
Trial 12              18         123        3          122
Trial 13              22         128        6          139
Trial 14              18         104        11         103
Trial 15              18         55         3          54
Trial 16              53         247        12         247
Trial 17              83         344        14         339
Trial 18              39         227        4          231
Trial 19              2          55         1          37
Trial 20              17         221        2          67
Trial 21              2          16         2          16
Trial 22              6          47         1          44
Trial 23              51         415        7          138
Trial 24              11         109        11         110
Trial 25              6          71         2          32
Trial 26              5          48         0          48
Trial 27              3          162        8          161
Trial 28              16         160        9          162
Trial 29              18         151        10         156
Trial 30              49         365        18         186
Trial 31              7          278        8          288
Trial 32              9          93         6          87
Trial 33              20         187        6          99
Trial 34              10         165        3          157
Trial 35              10         104        2          102
```

```
Trial 36              10          100         3           107
Trial 37              13          96          2           26
Trial 38              58          278         4           91
Trial 39              26          149         3           150
Trial 40              19          181         5           175
Trial 41              30          151         1           37
Trial 42              7           129         5           129
Trial 43              7           76          4           78
Trial 44              16          211         6           204
Trial 45 & 46         1           44          0           43
Trial 47              39          159         4           40
Trial 48              16          43          5           42
Trial 49 & 50         23          241         5           84
Trial 51              13          87          1           88
Trial 52              20          119         2           38
Trial 53              26          132         2           45
Trial 54              9           86          4           82
Trial 55              7           88          3           90
Trial 56              7           85          1           88
Trial 57              9           100         5           108
Trial 58              11          86          5           83
Trial 59              4           103         3           99
Trial 60              5           94          5           93
Trial 61              7           96          3           97
Trial 62              16          135         1           69
Trial 63              10          97          0           91
Trial 64              6           92          3           96
Trial 65              10          94          2           95
Trial 66              32          315         3           152
Trial 67              62          266         5           92
Trial 68              13          72          3           76
Trial 69              15          83          1           82
Trial 70              21          238         5           80
Trial 71              23          180         9           68
Trial 72              10          100         6           104
Trial 73              22          249         3           83



;run;



********** ANALYSIS
********************************************************************************
*********;
  %macro SparseMA(dataset=);

       ********* Prepare data sets in different configurations
****************************************;
       * Data set with one line per study;
         data one&dataset;
              set &dataset;
         run;

       * Data set with two lines per study for all procedures that use the
events/trial syntax;
         data help&dataset;
              set &dataset;
```

```
            by study;
            do i=1 to 2;
               output;
            end;
         run;

         data double&dataset;
            set help&dataset;
            int=1;
            if i=1 then do; noutcomes=st;ntrials=nt;treatment=1;control=0;end;
            if i=2 then do; noutcomes=sc;ntrials=nc;treatment=0;control=1;end;
         run;

       * "Exploded" data set with one line for every patient;
         data exploded&dataset;
            set double&dataset;
            do j=1 to ntrials;
               if j <= noutcomes then outcome=1;
               if j >  noutcomes then outcome=0;
               status=2-outcome;
               output;
           end;
         run;

       ********* Describe sparseness
*****************************************;
         proc freq data=&dataset;
            tables sparse;
            title"&dataset, Description of sparseness";
            format sparse sparse.;
         run;
```

AED, Description of sparseness

The FREQ Procedure

sparse	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Regular	68	95.77	68	95.77
Single-zero control	3	4.23	71	100.00

Meta-analysis using beta-binomial method

```
*** Beta-binomial model ***;
          ods select none;
          proc nlmixed data=double&dataset df=10000;
             * Give starting values for the model parameters;
               parms rho=0.1 atilde=-5 btilde=-0.1;

             * Define LogLikelihood function;
               mu= exp(atilde + btilde*treatment)/ (1 + exp(atilde +
btilde*treatment));
```

```
              * ALPHA and BETA are the parameters of the underlying beta
distribution;
                alpha=mu*(1-rho)/rho;
                beta=(1-mu)*(1-rho)/rho;

                ll= lgamma(ntrials+1)+lgamma(noutcomes+alpha)+lgamma(ntrials-
noutcomes+beta)+lgamma(alpha+beta)
                   -lgamma(noutcomes+1)-lgamma(ntrials-noutcomes+1)-
lgamma(ntrials+alpha+beta)-lgamma(alpha)
                   -lgamma(beta);

                model noutcomes ~ general(ll);

              * Additional Estimates;
                estimate "LogOR" btilde;

                ods output
AdditionalEstimates=LogOR_BBIN_temp(where=(Label="LogOR")
rename=(Estimate=LogOR_BBIN

StandardError=SE_LogOR_BBIN));
                title"&dataset, OR, Beta-binomial model, NLMIXED";

           run;
           ods select all;

           data OR_BBIN(keep=OR_BBIN CI95L_OR_BBIN CI95U_OR_BBIN SE_LogOR_BBIN);
                set LogOR_BBIN_temp;
                CI95L_LogOR_BBIN =  LogOR_BBIN - probit(0.975)* SE_LogOR_BBIN;
                CI95U_LogOR_BBIN =  LogOR_BBIN + probit(0.975)* SE_LogOR_BBIN;

                OR_BBIN=exp(LogOR_BBIN);
                CI95L_OR_BBIN=exp(CI95L_LogOR_BBIN);
                CI95U_OR_BBIN=exp(CI95U_LogOR_BBIN);
           run;
           proc print data=OR_BBIN noobs;
                var OR_BBIN CI95L_OR_BBIN CI95U_OR_BBIN;
                format OR_BBIN CI95L_OR_BBIN CI95U_OR_BBIN 5.3;
                 run;
```

AED, OR, Beta-binomial model, NLMIXED

OR_BBIN	CI95L_OR_BBIN	CI95U_OR_BBIN
2.571	2.063	3.204

B. Discontinuations due to lack of effect

SAS code, dataset and results

```
options pagesize=80 linesize=160 nodate nonumber ;

  proc format;
       value treat 0="Placebo" 1=" Drug ";
       value event 0="No " 1=" Yes";
```

```
      value sparse 1="Regular"  2="Single-zero treatment" 3="Single-zero
control" 4="Double-zero";
  run;

********** READING DATA SETS
********************************************************************************
*********************************************;

data LoE;
     input study $13. st nt sc nc;
     TotalNumber=nt+nc;
     index=1;
   * Define Sparseness;
     sparse=1;
     if (st=0 and sc ne 0) then sparse=2;
     if (sc=0 and st ne 0) then sparse=3;
     if st=0 and sc=0 then sparse=4;
     format sparse sparse.;
     cards;
```

Trial 01	8	53	11	52
Trial 02	5	89	12	88
Trial 03	72	390	30	126
Trial 04	5	103	10	70
Trial 05	7	119	8	75
Trial 06	10	264	12	90
Trial 07	28	264	23	89
Trial 08	5	342	4	115
Trial 09	6	274	7	93
Trial 10	6	293	4	99
Trial 11	1	136	3	142
Trial 12	5	123	10	122
Trial 13	7	128	19	139
Trial 14	9	104	13	103
Trial 15	0	55	3	54
Trial 16	5	247	2	247
Trial 17	3	344	8	339
Trial 18	1	227	0	231
Trial 21	1	16	1	16
Trial 23	3	415	1	138
Trial 24	18	109	23	110
Trial 25	10	71	8	32
Trial 26	6	48	19	48
Trial 27	8	162	18	161
Trial 28	3	160	10	162
Trial 29	3	151	8	156
Trial 30	8	365	12	186
Trial 31	26	278	101	288
Trial 32	4	93	6	87
Trial 33	9	187	6	99
Trial 34	6	165	22	157
Trial 35	7	104	11	102
Trial 36	5	100	14	107
Trial 37	16	96	4	26
Trial 38	41	278	25	91
Trial 39	11	149	28	150
Trial 40	1	181	4	175
Trial 41	22	151	6	37
Trial 42	8	129	27	129

```
Trial 43              5          76          10          78
Trial 44              5          211         9           204
Trial 45 & 46         1          44          5           43
Trial 47              5          159         4           40
Trial 48              8          43          8           42
Trial 49 & 50         19         241         11          84
Trial 51              13         87          18          88
Trial 52              5          119         2           38
Trial 53              7          132         5           45
Trial 54              6          86          9           82
Trial 55              1          88          4           90
Trial 56              1          85          6           88
Trial 57              0          100         5           108
Trial 58              0          86          0           83
Trial 59              1          103         2           99
Trial 60              3          94          2           93
Trial 61              1          96          2           97
Trial 62              4          135         4           69
Trial 63              3          97          2           91
Trial 65              3          94          2           95
Trial 66              4          315         23          152
Trial 67              15         266         14          92
Trial 68              3          72          16          76
Trial 69              7          83          10          82
Trial 70              17         238         4           80
Trial 71              14         180         7           68
Trial 72              5          100         22          104
Trial 73              28         249         13          83

;run;



********** ANALYSIS
*************************************************************************
*********;
  %macro SparseMA(dataset=);

       ********* Prepare data sets in different configurations
****************************************;
       * Data set with one line per study;
         data one&dataset;
              set &dataset;
         run;

       * Data set with two lines per study for all procedures that use the
events/trial syntax;
         data help&dataset;
              set &dataset;
              by study;
              do i=1 to 2;
                 output;
              end;
         run;

         data double&dataset;
              set help&dataset;
              int=1;
              if i=1 then do; noutcomes=st;ntrials=nt;treatment=1;control=0;end;
```

```
            if i=2 then do; noutcomes=sc;ntrials=nc;treatment=0;control=1;end;
         run;

       * "Exploded" data set with one line for every patient;
         data exploded&dataset;
              set double&dataset;
              do j=1 to ntrials;
                 if j <= noutcomes then outcome=1;
                 if j >  noutcomes then outcome=0;
                 status=2-outcome;
                 output;
             end;
         run;

       ********* Describe sparseness
****************************************;
         proc freq data=&dataset;
              tables sparse;
              title"&dataset, Description of sparseness";
              format sparse sparse.;
         run;
```

LoE, Description of sparseness

The FREQ Procedure

sparse	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Regular	63	94.03	63	94.03
Single-zero treatment	2	2.99	65	97.01
Single-zero control	1	1.49	66	98.51
Double-zero	1	1.49	67	100.00

```
*** Beta-binomial model ***;
          ods select none;
           proc nlmixed data=double&dataset df=10000;
               * Give starting values for the model parameters;
                 parms rho=0.1 atilde=-5 btilde=-0.1;

               * Define LogLikelihood function;
                 mu= exp(atilde + btilde*treatment)/ (1 + exp(atilde +
btilde*treatment));

               * ALPHA and BETA are the parameters of the underlying beta
distribution;
                 alpha=mu*(1-rho)/rho;
                 beta=(1-mu)*(1-rho)/rho;

                 ll=
lgamma(ntrials+1)+lgamma(noutcomes+alpha)+lgamma(ntrials-
noutcomes+beta)+lgamma(alpha+beta)
                    -lgamma(noutcomes+1)-lgamma(ntrials-noutcomes+1)-
lgamma(ntrials+alpha+beta)-lgamma(alpha)
```

```
                   -lgamma(beta);

                model noutcomes ~ general(ll);

              * Additional Estimates;
                estimate "LogOR" btilde;

                ods output
AdditionalEstimates=LogOR_BBIN_temp(where=(Label="LogOR")
rename=(Estimate=LogOR_BBIN

StandardError=SE_LogOR_BBIN));
                title"&dataset, OR, Beta-binomial model, NLMIXED";

           run;
           ods select all;

           data OR_BBIN(keep=OR_BBIN CI95L_OR_BBIN CI95U_OR_BBIN
SE_LogOR_BBIN);
                set LogOR_BBIN_temp;
                CI95L_LogOR_BBIN =  LogOR_BBIN - probit(0.975)*
SE_LogOR_BBIN;
                CI95U_LogOR_BBIN =  LogOR_BBIN + probit(0.975)*
SE_LogOR_BBIN;

                OR_BBIN=exp(LogOR_BBIN);
                CI95L_OR_BBIN=exp(CI95L_LogOR_BBIN);
                CI95U_OR_BBIN=exp(CI95U_LogOR_BBIN);
           run;
           proc print data=OR_BBIN noobs;
                var OR_BBIN CI95L_OR_BBIN CI95U_OR_BBIN;
                format OR_BBIN CI95L_OR_BBIN CI95U_OR_BBIN 5.3;
           run;
```

LoE, OR, Beta-binomial model, NLMIXED

OR_BBIN	CI95L_OR_BBIN	CI95U_OR_BBIN
0.561	0.424	0.743

Supplementary Document C: Publication bias check using funnel plots

Figure 1: Funnel plot for overall drop-out rate (acceptability).

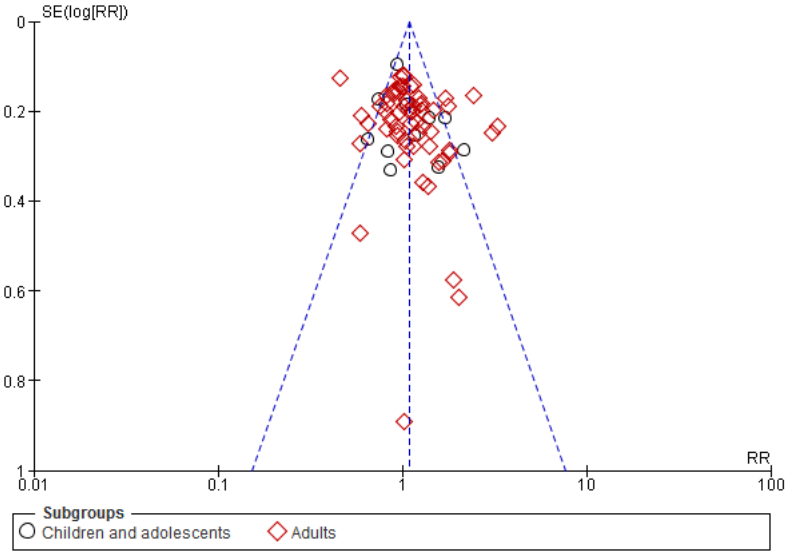


Figure 2: Funnel plot for drop-out rates due to adverse events (tolerability)

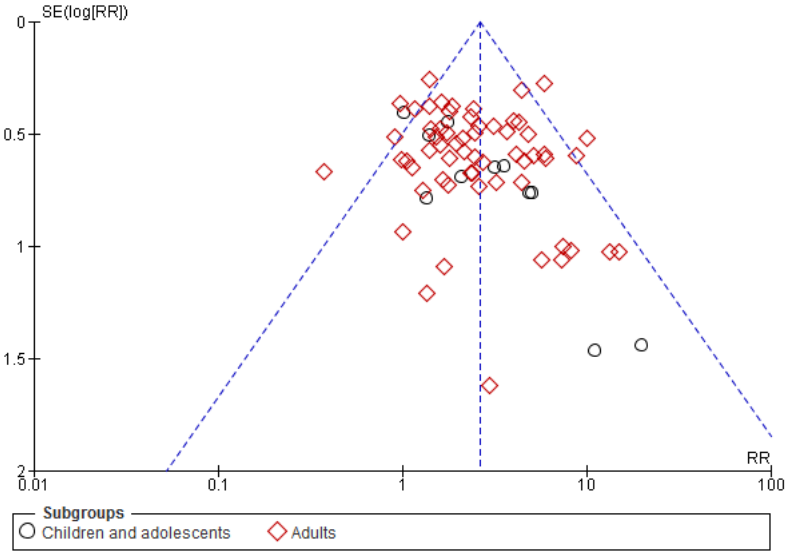
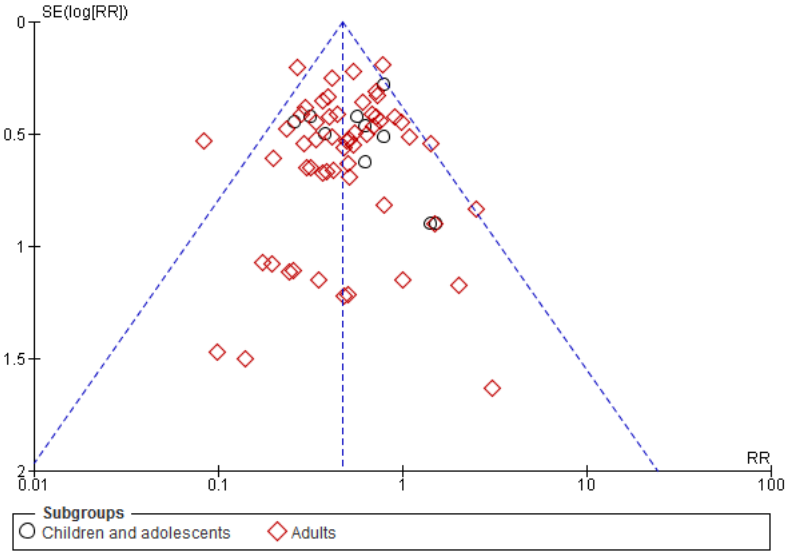


Figure 3: Funnel plot for drop-out rates due to lack of effect



Appendices for research article 4:

Supplementary Document A – Complete results of the comparison of the SF-36 and EQ-5D outcomes in CSRs and publications from companies

Supplementary Document B – Samples of correspondence with the companies

Supplementary Document C – Systematic searches to identify trial publications and their results

Supplementary Document A – Systematic searches to identify trial publications and their results

Search strategies for systematic searches undertaken for identifying literature for the included trials

Medline and Embase using OVID interface and Cochrane Central Register of Controlled Trials (CENTRAL) – example MEDLINE

- **duloxetine (major depressive disorder)** – list of articles taken from Maund E, Tendal B, Hróbjartsson A, Jørgensen KJ, Lundh A, Schroll J et al. Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications. BMJ 2014; 348:g3555.
- **duloxetine (urinary incontinence)**
    1. randomized controlled trial.pt.
    2. controlled clinical trial.pt.
    3. randomized.ab.
    4. placebo.ab.
    5. drug therapy.fs.
    6. randomly.ab.
    7. trial.ab.
    8. groups.ab.
    9. or/1-8
    10. exp animals/ not humans.sh.
    11. 9 not 10
    12. exp urinary incontinence/
    13. incontinence pads/
    14. urodynamics/
    15. urinary sphincter, artificial/
    16. urinary catheterization/
    17. parasympatholytics/
    18. exp bladder fistula/
    19. toilet training/
    20. cutaneous fistula/
    21. vaginal fistula/

22. vesicovaginal fistula/

23. "pelvic floor/

24. cystitis, interstitial/

25. toilet$.tw.

26. (incontinen$ or continen$).tw.

27. urodynamic$.tw.

28. nycturia.tw.

29. ((vesic$ or bladder or vagina$) adj5 (support$ or prosthes$)).tw.

30. (bladder adj5 (train$ or retrain$).tw.

31. interstitial cystitis.tw.

32. (fistula$ adj5 (bladder or vesic$ or bladder-vagina$ or urin$ or vagina$ or uretero-vagina$ or vesico-uterine or urogenital)).tw.

33. ((urin$ or bladder) adj5 sphincter$).tw.

34. ((bladder or detrusor or vesic$) adj5 (instability or stab$ or unstable or irritab$ or hyperreflexia or dys?ynerg$ or dyskinesia)).tw.

35. (void$ adj5 (prompt$ or diar$)).tw.

36. urethral syndrome.tw.

37. (urethra$ adj2 sphincter$).tw.

38. (bladder adj2 neck).tw.

39. (urin$ adj2 (leak$ or urge$ or frequen$)).tw.

40. (fistula adj5 genitourin$).tw.

41. perineomet$.tw.

42. interferential.tw.

43. marshall-marchetti-krantz.tw.

44. mmk.tw.

45. burch.tw.

46. ((bladder or neck or vesic$) adj5 suspen$).tw.

47. colposuspension$.tw.

48. guittes.tw.

49. colporrhaphy.tw.

50. pereyra.tw.

51. urethrosuspension$.tw.

52. cystoplast$.tw.

53. urethropex$.tw.

54. lyodura$.tw.

55. colpoperineoplast$.tw.

56. urethrocervicopex$.tw.

57. sling procedure$.tw.

58. stamey.tw.

59. (pelvic adj5 rehabilit$).tw.

60. raz.tw.

61. urinary fistula/

62. dribbl$.tw.

63. diaper$.tw.

64. bladder, neurogenic/

65. (bladder adj ulcer$).tw.

66. (hunner adj ulcer$).tw.

67. (vesic$ adj (neck$ or cervi$)).tw.

68. cystostomy.tw.

69. cystostomy/

70. vesicostomy.tw.

71. colporraphy.tw.

72. (fistula$ adj (urethra$ or colovesic$ or cystocol$ or cystovagina$ or vagino$)).tw.

73. sling$ procedure$.tw.

74. (pelvi$ adj5 rehabilit$).tw.

75. ((bladder or detrusor or vesic$) adj5 (instability or stab$ or unstable or irritab$ or irritat$ or hyperreflex$ or dys?ynerg$ or dyskines$ or hyperactiv$)).tw.

76. (urine adj5 extravasation).tw.

77. ((bladder or detrusor) adj overactiv$).tw.

78. ((urin$ or bladder or urethra) adj (prosthes$ or endoprosthes$)).tw.

79. (detrusor adj sphincter$).tw.

80. (spinal adj2 bladder$).tw.

81. (bladder$ adj2 (neuropath$ or neurogen$ or neurolog$)).tw.

82. 71 bodyworn$.tw.

83. 72 underpad$.tw.

84. or/10-81

85. (duloxetine or Yentreve).mp.

86. 11 and 84 and 85

87. remove duplicates from 86

- **duloxetine (fibromyalgia)**
  1. randomized controlled trial.pt.
  2. controlled clinical trial.pt.
  3. randomized.ab.
  4. placebo.ab.
  5. drug therapy.fs.
  6. randomly.ab.
  7. trial.ab.
  8. groups.ab.
  9. or/1-8
  10. exp animals/ not humans.sh.
  11. 9 not 10
  12. fibromyalgia.mp.
  13. (duloxetine or Cymbalta).mp.
  14. 11 and 12 and 13
  15. remove duplicates from 14
- **duloxetine (diabetic peripheral neuropathic pain)**
  1. randomized controlled trial.pt.
  2. controlled clinical trial.pt.
  3. randomized.ab.
  4. placebo.ab.
  5. drug therapy.fs.
  6. randomly.ab.
  7. trial.ab.

8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Diabetes Mellitus/
13. diabet$.mp.
14. exp diabetes mellitus, non-insulin-dependent/
15. or/12-14
16. neuropath$.mp.
17. exp Peripheral Nervous System Diseases/
18. polyneuropath$.mp.
19. or/16-18
20. exp diabetic neuropathies/
21. diabetic neuropath$.mp.
22. diabetic polyneuropath$.mp.
23. or/20-22
24. 15 or 19 or 23
25. (duloxetine or Cymbalta).mp.
26. 11 and 24 and 25
27. remove duplicates from 26

- **paroxetine (MDD)**
    1. randomized controlled trial.pt.
    2. controlled clinical trial.pt.
    3. randomized.ab.
    4. placebo.ab.
    5. drug therapy.fs.
    6. randomly.ab.
    7. trial.ab.
    8. groups.ab.
    9. or/1-8
    10. exp animals/ not humans.sh.

11. 9 not 10

12. (depression or depressive or mood disorder* or affective disorder* or bipolar).ti,ab,id,sh,tm.

13. (paroxetine or Seroxat or Paxil).mp.

14. 11 and 12 and 13

15. remove duplicates from 14

- **paroxetine (SP)**
  1. randomized controlled trial.pt.
  2. controlled clinical trial.pt.
  3. randomized.ab.
  4. placebo.ab.
  5. drug therapy.fs.
  6. randomly.ab.
  7. trial.ab.
  8. groups.ab.
  9. or/1-8
  10. exp animals/ not humans.sh.
  11. 9 not 10
  12. (social phobia or social anxiety disorder).ti,ab,id,sh,tm.
  13. (paroxetine or Seroxat or Paxil).mp.
  14. 11 and 12 and 13
  15. remove duplicates from 14
- **paroxetine (PTSD)**
  1. randomized controlled trial.pt.
  2. controlled clinical trial.pt.
  3. randomized.ab.
  4. placebo.ab.
  5. drug therapy.fs.
  6. randomly.ab.
  7. trial.ab.
  8. groups.ab.

9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Stress Disorders, Traumatic/
13. ((post-traumatic or post traumatic or posttraumatic) and disorder*).tw.
14. PTSD.tw.
15. or/12-14
16. (paroxetine or Seroxat or Paxil).mp.
17. 11 and 15 and 16
18. remove duplicates from 17

- **paroxetine (GAD)**
    1. randomized controlled trial.pt.
    2. controlled clinical trial.pt.
    3. randomized.ab.
    4. placebo.ab.
    5. drug therapy.fs.
    6. randomly.ab.
    7. trial.ab.
    8. groups.ab.
    9. or/1-8
    10. exp animals/ not humans.sh.
    11. 9 not 10
    12. ("Generalized Anxiety" or "Generalised Anxiety" or GAD).ti,ab,id,sh,tm.
    13. (paroxetine or Seroxat or Paxil).mp.
    14. 11 and 12 and 13
    15. remove duplicates from 14
- **sertraline (SP)**
    1. randomized controlled trial.pt.
    2. controlled clinical trial.pt.
    3. randomized.ab.
    4. placebo.ab.

5. drug therapy.fs.

6. randomly.ab.

7. trial.ab.

8. groups.ab.

9. or/1-8

10. exp animals/ not humans.sh.

11. 9 not 10

12. (social phobia or social anxiety disorder).ti,ab,id,sh,tm.

13. (sertraline or Zoloft).mp.

14. 11 and 12 and 13

15. remove duplicates from 14

Table 1: List of potential journal articles identified through searches and the results on SF-36 and EQ-5D

Note - it was not clear whether the publications were matched correctly to the trials due to poor article indexing and poor methodological descriptions within the articles (nor were all the relevant articles were retrieved)

Trial	Trial name	Drug	HRQoL type	Indication	Journal article (data availability)	Full References and comments
1	HMAQa	duloxetine (active comparator fluoxetine)	SF-36	MDD	Goldstein 2002[1] No mention of SF-36 in methods and no results for SF-36	1. Goldstein, D. J., Mallinckrodt, C., Lu, Y., & Demitrack, M. A. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. The Journal of clinical psychiatry, 2002:63(3), 225-231.
2	HMAQb	duloxetine (active comparator fluoxetine)	SF-36	MDD	No publication found	
3	HMAH	duloxetine	SF-36	MDD	No publication found	
4	SAAW	duloxetine	SF-36	SUI in Women	Norton 2002[2] Bump 2003[3] No mention of SF-36 in methods and no results for SF-36 (only results of I-QoL are available).	2. Norton, P. A., Zinner, N. R., Yalcin, I., Bump, R. C., and Duloxetine Urinary Incontinence Study Group. Duloxetine versus placebo in the treatment of stress urinary incontinence. American journal of obstetrics and gynecology 2002;187(1)40-48. 3. Bump, R. C., Norton, P. A., Zinner, N. R., Yalcin, I., and Duloxetine Urinary Incontinence Study Group. Mixed urinary incontinence symptoms: urodynamic findings, incontinence severity, and treatment response. Obstetrics & Gynecology 2003; 102(1), 76-83. *CSR mentions: Yalcin I. Correlation bet ween patient perceptions of severity and subjective and objective measures of stress urinary incontinence. Urology l 65(5): I 03. But this was unavailable to us*
5	SAAB	duloxetine	SF-36	SUI (or mixed) in Women	No publication found	
6	HMBOa	duloxetine	SF-36	Fibromyalgia with	Arnold 2004[4] No results on SF-36	4. Arnold, LM, Lu Y, Crofford,LJ, Wohlreich M, Detke MJ, Iyengar S, and Goldstein DJ. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients

Trial	Trial name	Drug	HRQoL type	Indication	Journal article (data availability)	Full References and comments
				or without MDD		with or without major depressive disorder. Arthritis & Rheumatism 2004;50(9)2974-2984.
7	HMAW	duloxetine	SF-36 and EQ-5D	DPNP	Goldstein 2005[5] Results of SF-36 component summary scores for PCS and MCS and individual domain scores available for bodily pain, general health and mental health. Utility scores for EQ-5D available.	5. Goldstein, D J., Lu Y, Detke MJ, Lee TC, and Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. Pain ;2005;116(1)109-118. *Two additional articles used data from this trial for further work (but no relevant results on SF-36 nor EQ-5D.* *a) Kajdasz 2007[1] was a pooled analysis that included data from HMAW* *b) Wu 2006 [2]was a cost effective analysis that appears to have included data from HMAW*
8	SBAM	duloxetine	EQ-5D	SUI in Women electing surgery for severe pure GSI	Cardozo 2004[6] No results of EQ-5D (results from I-QoL are available).	6. Cardozo, L., Drutz, H. P., Baygani, S. K., Bump, R. C., and Duloxetine Severe UI Study Group. Pharmacological treatment of women awaiting surgery for stress urinary incontinence. Obstetrics & Gynecology 2004;104(3):511-519.
9	Protocol 377	paroxetine	EQ-5D	MDD	Berard 2006 [7] No results of EQ-5D	7. Berard R, Fong R, Carpenter DJ, Thomason C, Wilkinson C. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. Journal of Child & Adolescent Psychopharmacology. 2006 Mar 1;16(1-2):59-75.
10	Protocol 595	paroxetine	EQ-5D	SP	Stein 2002 [8] results only for EQ-5D VAS - utility scores missing	8. Stein DJ, Versiani M, Hair T, Kumar R. Efficacy of paroxetine for relapse prevention in social anxiety disorder: a 24-week study. Archives of General Psychiatry. 2002 Dec 1;59(12):1111-8.

[1] *Kajdasz 2007 - Kajdasz, D.K., Iyengar, S., Desaiah, D., Backonja, M.M., Farrar, J.T., Fishbain, D.A., Jensen, T.S., Rowbotham, M.C., Sang, C.N., Ziegler, D. and McQuay, H.J., 2007. Duloxetine for the management of diabetic peripheral neuropathic pain: evidence-based findings from post hoc analysis of three multicenter, randomized, double-blind, placebo-controlled, parallel-group studies. Clinical Therapeutics, 29(11), pp.2536-2546.*

[2] *Wu 2006 – Wu, E.Q., Birnbaum, H.G., Mareva, M.N., Le, T.K., Robinson, R.L., Rosen, A. and Gelwicks, S., 2006. Cost-effectiveness of duloxetine versus routine treatment for US patients with diabetic peripheral neuropathic pain. The Journal of pain, 7(6), pp.399-407.*

Trial	Trial name	Drug	HRQoL type	Indication	Journal article (data availability)	Full References and comments
11	Protocol 648	paroxetine	EQ-5D	PTSD	Tucker 2001 [9] No results of EQ-5D (Only results for other efficacy outcomes and SDS noted.)	9. Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Pitts CD. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. The Journal of clinical psychiatry. 2001 Nov 1;62(11):1-478.
12	Protocol 651	paroxetine	EQ-5D	PTSD	Marshall 2001 [10] No results of EQ-5D (Only results for other efficacy outcomes and SDS noted.)	10. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety ofparoxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psychiatry 2001; 158: 1982–8.
13	Protocol 627	paroxetine	EQ-5D	PTSD	No publication found	
14	Protocol 646	paroxetine	EQ-5D	GAD	Stocchi 2003 [11] No results of EQ-5D (Only results for other efficacy outcomes and SDS noted.)	11. Stocchi F, Nordera G, Jokinen RH, Lepola UM, Hewett K, Bryson H, Iyengar MK. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. The Journal of clinical psychiatry. 2003 Mar;64(3):250-8.
15	STL-NY-94-004	sertraline	SF-36 and EQ-5D	SP	Van Ameringen 2001[12] No results of SF-36 nor EQ-5D (results from Sheehan Disability Scale available)	12 Van Ameringen, M. A., Lane, R. M., Walker, J. R., Bowen, R. C., Chokka, P. R., Goldner, E. M, Johnston DG, et al. Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. American Journal of Psychiatry 2001;158(2)275-281.

Notes: DPNP: diabetic peripheral neuropathic pain; GAD: generalized anxiety disorder; GSI: genuine stress incontinence; MDD: major depressive disorder; PTSD: posttraumatic stress disorder; SDS: Sheehan Disability Scale; SP: social phobia; SUI: stress urinary incontinence

Supplementary Document B – Complete results of the comparison of the SF-36 and EQ-5D outcomes in CSRs, available online and through publications from industry

Table 1: Journal articles for the included trials received from industry

Drug	Protocol	HRQoL type	No. of publications	All references/ additional information received
From Eli Lilly and Company				
DLX	HMAQa	SF-36	1	• Goldstein DJ, Mallinckrodt C, Lu Y, Demitrack MA. Duloxetine in the treatment of major depressive disorder: A double-blind clinical trial. J Clin Psych. 2002;63(3):225-231. http://www.psychiatrist.com/privatepdf/2002/v63n03/v63n0309.pdf
DLX	HMAQb	SF-36	1	• Nemeroff CB, Schatzberg AF, Goldstein DJ, Detke MJ, Mallinckrodt C, Lu Y, Tran PV. Duloxetine for the Treatment of Major Depressive Disorder. Psychopharmacol Bull 2002;36(4):106-32. http://www.ncbi.nlm.nih.gov/pubmed/12858150
DLX	HMAH	SF-36	0	F1J-MC-HMAH and F1J-MC-SAAB are unpublished, although summaries of results are available via http://www.lillytrials.com/results/results.html
DLX	SAAW	SF-36	3	• Yalcin I, Viktrup L. Comparison of physician and patient assessments of incontinence severity and improvement. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Nov;18(11):1291-5. http://dx.doi.org/10.1007/s00192-007-0326-8 • Viktrup L, Yalcin I. Duloxetine Treatment of Stress Urinary Incontinence in Women: Effects of Demographics, Obesity, Chronic Lung Disease, Hypoestrogenism, Diabetes Mellitus, and Depression on Efficacy. Eur J Obstet Gynecol Reprod Biol. 2007;133(1):105-13. http://dx.doi.org/10.1016/j.ejogrb.2006.05.003 • Hurley D, Turner C, Baygani S,Yalcin I, Viktrup L. Duloxetine for the Treatment of SUI in Women: An Integrated Analysis of Safety. Eur J Obstet Gynecol Reprod Biol. 2006;125(1):120-8. http://dx.doi.org/10.1016/j.ejogrb.2005.08.006
DLX	SBAMa	EQ-5D	1	• Cardozo L, Drutz HP, Baygani SK, Bump RC. Pharmacological treatment of women awaiting surgery for stress urinary incontinence. Obstet Gynecol. 2004 Sep;104(3):511-9.
DLX	SAAB	SF-36	0	F1J-MC-HMAH and F1J-MC-SAAB are unpublished, although summaries of results are available via http://www.lillytrials.com/results/results.html

Drug	Protocol	HRQoL type	No. of publications	All references/ additional information received
DLX	HMBOa	SF-36	2	• Arnold LM, Lu Y, Crofford LJ, Wohlreich M, Detke MJ, Iyengar S, Goldstein DJ, Duloxetine Fibromyalgia Trial Group. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthrit Rheum. 2004;50(9):2974-2984. http://dx.doi.org/10.1002/art.20485 • Arnold LM, Pritchett YL, D'Souza DN, Kajdasz DK, Iyengar S, Wernicke JF. Duloxetine for the Treatment of Fibromyalgia in Women: Pooled Results From Two Randomized, Placebo-Controlled Clinical Trials. J Womens Health. 2007;16(8):1145-56. http://dx.doi.org/10.1089/jwh.2006.0213
DLX	HMAWa	SF-36 & EQ-5D	12	• Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine versus placebo in patients with painful diabetic neuropathy. Pain. 2005;116:109-118. http://dx.doi.org/10.1016/j.pain.2005.03.029 • Wernicke JF, Raskin J, Rosen A, Pritchett YL, D'Souza DN, Iyengar S, Knopp K, Le TK. Duloxetine in the long-term management of diabetic peripheral neuropathic pain: an openlabel, 52-week extension of a randomized controlled clinical trial. Curr Ther Clin Exp.2006;67:283-304. http://dx.doi.org/10.1016/j.curtheres.2006.10.001 • Yuen E, Gueorguieva I, Aarons L. Handling Missing Data in a Duloxetine Population Pharmacokinetic/Pharmacodynamic Model - Imputation Methods and Selection Models. Pharm Res. 2014;May 3:[epub ahead of print]. http://dx.doi.org/10.1007/s11095-014-1380-9 • Hall JA, Wang F, Oakes TM, Utterback BG, Crucitti A, Acharya N. Safety and tolerability of duloxetine in the acute management of diabetic peripheral neuropathic pain: analysis of pooled data from three placebo-controlled clinical trials. Expert Opin Drug Saf. 2010;9(4):525-37. http://dx.doi.org/10.1517/14740338.2010.484418 • Wasan AD, Ossanna MJ, Raskin J, Wernicke JF, Robinson MJ, Hall JA, Edwards SE, Lipsius S, Meyers AL, McCarberg WH. Safety and efficacy of duloxetine in the treatment of diabetic peripheral neuropathic pain in older patients. Curr Drug Safety. 2009;4(1):22-9. http://dx.doi.org/10.2174/157488609787354404 • Fishbain DA, Hall JA, Risser RC, Gonzales JS. Does pain cause the perception of fatigue in patients with chronic pain? Findings from studies for management of diabetic peripheral neuropathic pain with duloxetine. Pain Pract. 2009;9(5):354-62. http://dx.doi.org/10.1111/j.1533-2500.2009.00294.x • Guastella V, Mick G. Strategies for the diagnosis and treatment of neuropathic pain secondary to diabetic peripheral sensory polyneuropathy. Diabetes Metab. 2009 Feb;35(1):12-9. http://dx.doi.org/10.1016/j.diabet.2008.09.003 • Wernicke JF, Prakash A, Kajdasz DK, Houston J. Safety and tolerability of duloxetine treatment of

Drug	Protocol	HRQoL type	No. of publications	All references/ additional information received
				diabetic peripheral neuropathic pain between patients with and without cardiovascular conditions. J Diabetes Complications. 2009;23(5):349-59. http://dx.doi.org/10.1016/j.jdiacomp.2008.07.004 • Fishbain DA, Hall J, Meyers AL, Gonzales J, Mallinckrodt C. Does pain mediate the pain interference with sleep problem in chronic pain? Findings from studies for management of diabetic peripheral neuropathic pain with duloxetine. J Pain Symptom Manage. 2008;36(6):639-47. http://dx.doi.org/10.1016/j.jpainsymman.2007.12.012 • Armstrong DG, Chappell AS, Le TK, Kajdasz DK, Backonja M, D'Souza DN, Russell JM. Duloxetine for the Management of Diabetic Peripheral Neuropathic Pain: Evaluation of Functional Outcomes. Pain Med. 2007;8(5):410-8. http://dx.doi.org/10.1111/j.1526-4637.2007.00276.x • Pritchett YL, McCarberg BH, Watkin JG, Robinson MJ. Duloxetine for the Management of Diabetic Peripheral Neuropathic Pain: Response Profile. Pain Med. 2007;8(5):397-409. http://dx.doi.org/10.1111/j.1526-4637.2007.00305.x • Fishbain D, Berman K, Kajdasz DK. Duloxetine for Neuropathic Pain Based on Recent Clinical Trials. Curr Pain Headache Rep. 2006;10(3):199-204. http://dx.doi.org/10.1007/s11916-006-0046-7
From GlaxoSmithKline (obtained through searching the GSK website using the ID given by the company)				
PAR	Protocol 648	EQ-5D	1	29060/648 • Tucker et al. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001; 62: (11): 860-868
PAR	Protocol 651	EQ-5D	1 + 4 conference abstracts (5)	29060/651 • Marshall et al. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psych. 2001; 158: 1982-1988 • Paroxetine in the treatment of post- traumatic stress disorder (ptsd). J. Davidson, D. J. Stei K. Hewett A. AdarnS H. Bryson K. Beebe C. Pitts L. Ruggerio M. Oldham K. Dillingham. 23rd Congress of the Collegium Internationale Neuropsychopharmacologicum (CINP) 6/23/2002 Montreal, QC; Canada • Post-traumatic stress disorder: remission rates following paroxetine treatment. Davidson, J R T, Hewett, K, Bryson, H, Oldham, M, Beebe, K, and Ruggiero, L 15th Congress of the European College of Neuropsychopharmacology (ECNP) 10/5/2002 Barcelona; Spain • Rates of ptsd symptom remission in patients treated with paroxetine. Davidson, J R T, Beebe, K L, Hewett, K, Pitts, C D, Adams, A, and Ruggiero, L D 155th Annual Meeting of the American Psychiatric Association 5/18/2002 Philadelphia, PA; USA

Drug	Protocol	HRQoL type	No. of publications	All references/ additional information received
				• Rernission in ptsd after paroxetine treatment. J.R. Davidson, K. Hewett M. Oldham A. Adams K. Beebe C. Pitts 12th World Congress of Psychiatry 8/24/2002 Yokohama; Japan
PAR	Protocol 627	EQ-5D	1	29060/627 • Stein DJ, Davidson J, Seedat S, Beebe K. Paroxetine in the treatment of post-traumatic stress disorder: pooled analysis of placebo-controlled studies. Expert Opin Pharmacother. 2003 Oct;4(10):1829-38
PAR	Protocol 646	EQ-5D	1 + 2 conference abstracts (3)	29060/646 • Stocchi et al. Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. J Clin Psychiatry 2003; 64 (3): 250-258 • Maintained efficacy of paroxetine in gad. Flbrizio Stocchi, G. Nordera R. jokinen U. Lepola H. Bryson 7th World Congress of Biological Psychiatry 7/1/2001 Berlin; Germany • Efficacy and tolerability of paroxetine for long term treatment of gad. Stocchi, F 154th Annual Meeting of the American Psychiatric Association 5/5/2001 New Orleans, LA; USA
PAR	Protocol 595	EQ-5D	1	29060/595 • Stein et al. Efficacy of paroxetine for relapse prevention in social anxiety disorder: a-24 week study. Arch Gen Psych. 2002; 59: 1111-1118.
PAR	Protocol 377	EQ-5D	1	29060/377 • Berard R, Fong R, Carpenter D, et al. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. Journal of Child & Adolescent Psychopharmacology. 16(1-2):59-75, 2006 Feb-Apr
From Pfizer				
SER	STL-NY-94-004	SF-36 & EQ-5D	0	None received

Table 2a: Complete results available on SF-36 from CSRs and/ or any data available online

Protocol	Intervention	Population in trial	Population for HRQoL at baseline	PCS score baseline	SD for PCS score baseline	PCS score mean change	SD for PCS score mean change	MCS score baseline	SD for MCS score baseline	MCS score mean change	SD for MCS score mean change
HMAQa	duloxetine	70	57	53.87	9.93	(-1.34)	7.97	22.67	7.83	14.42	15.4
	fluoxetine	33	29	51.89	12	(-0.02)	7.5	24.9	6.92	12.44	14.28
	placebo	70	59	52.54	10.6	1.3	8.25	23.65	7.15	8.28	11.86
HMAQb	duloxetine	82	69	53.16	10.51	(-0.47)	7.37	23.29	8.98	15.21	14.53
	fluoxetine	37	30	50.67	10.08	1.03	9.02	24.44	8.2	12.62	15.51
		75	65	51.85	9.68	(-1.29)	8.7	24.9	7.5	10.71	13.03
HMAH	duloxetine	No data in tables on SF-36, only have detailed data on safety in CSR. No mention of SF-36 in online report									
SAAW	duloxetine			Lilly report has data on results for I-QOL (efficacy measure), mentions SF-36 has been evaluated as outcomes section but no results							
	20mg/day	138	132	Only raw data on the eight different domains available in CSR							
	40mg/day	137	130								
	80mg/ day	140	130								
SAAB	duloxetine	No results of SF-36 in CSR, only listed in protocol and study design description. No mention of SF-36 in Lilly online report.									
HMBOa	duloxetine	104	91	29.25	8.82	5.49	SE 0.81	46.29	11.75	2.98	SE 1.04
	placebo	103	92	30.27	8.04	2.53	SE 0.80	43.95	10.3	0.52	SE 1.05
HMAW	duloxetine	Tables available for SF-36 but not with titles so cannot identify what table is what domain. Lilly report has data on results for other efficacy measures, mentions SF-36 has been evaluated as noted in the outcomes section but no results.									

Protocol	Intervention	Population in trial	Population for HRQoL at baseline	PCS score baseline	SD for PCS score baseline	PCS score mean change	SD for PCS score mean change	MCS score baseline	SD for MCS score baseline	MCS score mean change	SD for MCS score mean change
	20QD	115	98	36.00	9.78	2.91	8.25	53.46	9.21	0.01	8.18
	60QD	114	101	35.76	11.24	5.1	7.07	53.9	9.21	0.5	7.74
	60BID	113	101	34.56	9.74	5.57	8.67	53.39	9.42	1.92	8.71
	placebo	115	102	35.04	9.71	3.38	8.19	53.92	9.92	(-1.31)	8.94
STL-NY-94-004	sertraline	135	125	Only raw data on the eight different domains available							

Note: MCS: mental component score; PCS: physical component score; SD: standard deviation; SE: standard error: QD (quaque die): once a day; BD: twice a day

Table 2b: Complete results available on SF-36 for two trials where only raw data on the eight different domains was available

Protocol	Intervention	Population in trial	Population for HRQoL at baseline	PF	RP	BP	GH	VT	SF	RE	MH
SAAW	duloxetine			**Baseline**							
	20mg/day	138	132	76.63	85.98	79.62	76.04	61.29	90.25	85.61	77.92
	40mg/day	137	130	77.33	84.36	79.81	77.39	60.9	89.71	89.23	79.62
	80mg/ day	140	130	79.12	87.69	78.25	78. 84	61.69	89.9	87.69	78.46
	placebo	138	132	76.84	84.66	76.17	76.65	58.46	92.23	90.15	79.86
	duloxetine			**End**							

Protocol	Intervention	Population in trial	Population for HRQoL at baseline	PF	RP	BP	GH	VT	SF	RE	MH
	20mg/day			81.86	84.28	78.94	74.94	60.2	90.25	86.87	80.36
	40mg/day			85.92	83.59	79.08	76.82	61.74	90.96	91.28	81.04
	80mg/ day			85.71	84.23	79.27	78.41	60.47	87.31	89.23	81.35
	placebo			83.36	87.12	78.79	73.9	59.09	91.38	90.4	78.67
				Baseline							
STL-NY-94-004	sertraline	135	125	93.12	88.2	82.78	75.61	49.27	67.7	70.67	56.73
	placebo	69	66	92.79	86.36	80.82	76.79	52.95	71.21	67.68	54.73
				End							
	sertraline			92.83	86.71	82.98	79.73	58.62	78.77	82.80	69.98
	placebo			92.24	86.19	83.18	77.75	57.74	67.54	76.62	62.69

PF: physical functioning; RP: physical role functioning; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE emotional role functioning; MH: mental health

Table 3: Complete results available on EQ-5D from CSRs and/ or any data available online

Protocol	Intervention	Number in I arm for HRQoL anlaysis	VAS baseline	SD for VAS baseline	EQ-5D VAS	EQ-5D SD for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
SBAM	duloxetine	Main report and tables have data for I-QoL and other but not EQ-5D and same in the online summary report								
HMAW	duloxetine		Missing EQ-5D VAS scale results							
	20mg/day	101					0.6	0.25	0.1	0.25
	60 QD	104					0.6	0.25	0.14	0.26
	60 BID	105					0.63	0.22	0.12	0.24
	placebo	107	Missing EQ-5D VAS scale results				0.63	0.25	0.06	0.26
Protocol 648	paroxetine	BL 151 wk 12 OC 87 wk 12 LOCF 101	62.27	1.71	Mean at 12 weeks OC 14.48 LOCF 12.51	OC 2.13 LOCF 2.01	OC 0.59	0.271	0.11	0.291
	placebo	BL 156 wk 12 OC 92 VAS and 91 utility wk 12 LOCF 106	62.74	1.73	OC 7.97 LOCF 6.12	OC 2.10 LOCF 2.10	0.58	0.281	0.10	0.288

Protocol	Intervention	Number in I arm for HRQoL anlaysis	VAS baseline	SD for VAS baseline	EQ-5D VAS	EQ-5D SD for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
Protocol 651	20mg	VAS 20mg 183 BL 100 OC 122 LOCF utility 20mg 181 BL 100 OC	60.18	1.52	Mean at 12 weeks OC 16.81 LOCF 13.18	OC 2.09 LOCF 2.06	0.58	0.282	0.14	0.249
	40mg	VAS 40mg 182 BL 100 OC 121 LOCF utility 40mg 181 BL 98OC	64.47	1.44	Mean at 12 weeks OC 11.28 LOCF 9.33	OC 2.06 LOCF 1.96	0.59	0.288	0.12	0.269
		VAS 185 BL 106 OC 128 LOCF utility 185 BL 106 OC	61.22	1.49	OC 12.29 LOCF 10.34	OC 2.22 LOCF 1.97	0.59	0.285	0.07	0.271

Protocol	Intervention	Number in I arm for HRQoL anlaysis	VAS baseline	SD for VAS baseline	EQ-5D VAS	EQ-5D SD for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
Protocol 627	paroxetine	VAS 156 baseline 120 LOCF 108 OC utility 158 baseline 107 OC	44.6	1.7	Mean at 12 weeks LOCF 17.9 OC 19.9	LOCF 2.3 OC 2.4	0.5	0.3	0.2	0.3
		VAS 143 baseline 110 LOCF 90 OC utility 162 baseline 103 OC	48.0	1.7	LOCF 13.3 OC 16.3	LOCF 2.4 OC 2.7	0.4	0.3	0.2	0.3
Protocol 377	paroxetine	130 at BL 120 at Wk12 OC	49.8	1.8	change 22.1 Not change but mean at w12 71.6	change SE 2.3 SE 2.0	Utility results missing			

Protocol	Intervention	Number in I arm for HRQoL anlaysis	VAS baseline	SD for VAS baseline	EQ-5D VAS	EQ-5D SD for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
	placebo	68 at BL 64 at w12	49.3	2.5	change 24.0 Not change but mean at wk12 72.1	change SE2.9 SE 2.7	Utility results missing			
Protocol 595	paroxetine	VAS 162 baseline 153 wk 36 utility 162 baseline 133 OC	Median no Mean 80.0	Range no SE 9 to 100	change 1.0 median difference 12.00	Range - 55 to 76	0.843	SE 0.0105	mean change (-0.007)	SE 0.115
	placebo	VAS 161 baseline 156 wk 36 utility 161 baseline 119 OC	Median no Mean 80.0	Range no SE 10 to 100	change (-6.5)	Range - 95 to 60	0.847	SE 0.0088	mean change (-0.108)	SE (0.0235)

Protocol	Intervention	Number in I arm for HRQoL anlaysis	VAS baseline	SD for VAS baseline	EQ-5D VAS	EQ-5D SD for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
Protocol 646	paroxetine	VAS 221 BL 189 OC 221 LOCF utility 221 BL 188 OC 221 LOCF	76.4	1	Change in Mean at 32 weeks OC 6.1 LOCF 2.6	OC 1.0 LOCF 1.5	0.8	SE not SD 0	OC 0 and LOCF (-0.0)	both 0
	placebo	VAS 229 BL 126 OC 229 LOCF utility 230 BL 127 OC 230 LOCF	77.3	1	Change in Mean at 32 weeks OC 1.3 LOCF (-10.9)	OC 1.2 LOCF 1.4	0.8	SE not SD 0	LOCF (-0.1) OC 0.0	both 0
STL-NY-94-004	sertraline	125	78.06	13.54	1.70	14.02	Utility results missing			
	placebo	66	78.55	12.59	(-0.89)	10.75	Utility results missing			

Note: BL: basline; LOCF: last observation carried forward; OC: observed cases; SD: standard deviation; SE: standard error; wk: week

Table 4a: Complete results available on SF-36 from journal publications (received from industry or searched using ID from GSK on their website)

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	PCS score baseline	SD for PCS score baseline	PCS score mean change	SD for PCS score mean change	MCS score baseline	SD for MCS score baseline	MCS score mean change	SD for MCS score mean change
HMAQa	Goldstein 2002	Duloxetine	70	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		placebo	70	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAQb	Nemeroff 2002	duloxetine	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAH	No publications identified or received from company											
SAAW	Hurley 2006	duloxetine	958	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	955	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SAAW	Viktrup 2007 (pooled study, includes data from SAAW)	Duloxetine	958	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	955	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SAAW	Yalcin 2007	DLX 20mg	138	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 40mg	137	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 80mg	140	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	138	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	PCS score baseline	SD for PCS score baseline	PCS score mean change	SD for PCS score mean change	MCS score baseline	SD for MCS score baseline	MCS score mean change	SD for MCS score mean change
SAAW	Bump 2003	DLX 20mg	138	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 40mg	137	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 80mg	140	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	138	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SAAW	Norton 2002	DLX 20mg	138	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 40mg	137	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 80mg	140	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	138	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SAAB	No publications identified or received from company											
HMBOa	Arnold 2004	Duloxetine	104	91	29.3	8.8	5.49	0.81 SE	46.3	11.8	2.98	1.04 SE
		Placebo	103	92	30.3	8.0	2.53	0.80 SE	44.0	10.3	0.52	1.05 SE
HMBOa	Arnold 2007	Duloxetine	326	297	28.85	8.04	5.20	0.49 SE	43.87	11.71	4.18	0.65 SE
		Placebo	212	192	29.30	7.60	2.71	0.57 SE	43.35	10.63	1.56	0.72 SE
HMAW-a	Armstrong 2007	DLX 60mg QD	344	275-277	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 60mg BD	341	253-256	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	270-272	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	PCS score baseline	SD for PCS score baseline	PCS score mean change	SD for PCS score mean change	MCS score baseline	SD for MCS score baseline	MCS score mean change	SD for MCS score mean change
HMAW-a	Fishbain 2006	DLX 60mg QD	344	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 60mg BD	341	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Fishbain 2008	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Fishbain 2009	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Goldstein 2005	DLX 20mg	115	98	N/A	N/A	3.67	0.78 SE	N/A	N/A	0.02	0.76 SE
		DLX 60mg QD	114	101	N/A	N/A	5.86	0.77 SE	N/A	N/A	0.63	0.76 SE
		DLX 60mg BD	113	101	N/A	N/A	5.85	0.76 SE	N/A	N/A	1.84	0.75 SE
		Placebo	115	102	N/A	N/A	3.94	0.77 SE	N/A	N/A	-1.09	0.75 SE
HMAW-a	Guastella 2009	Duloxetine	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Hall 2010	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Pritchett 2007	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	PCS score baseline	SD for PCS score baseline	PCS score mean change	SD for PCS score mean change	MCS score baseline	SD for MCS score baseline	MCS score mean change	SD for MCS score mean change
		Placebo	399	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Wasan 2009	DLX 60mg QD	344	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 60mg BD	341	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Wernicke 2006	Duloxetine	222	202	40.8	9.6	0.7	0.6 SE	55.4	8.0	-2.5	0.7 SE
HMAW-a	Wernicke 2006	Placebo	115	107	40.1	11.0	-1.1	0.8 SE	54.6	8.9	-3.1	0.9 SE
HMAW-a	Wernicke 2009	DLX 60mg QD	344	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 60mg BD	341	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Yuen 2014	Duloxetine	779	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	327	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Kajdasz 2007	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Wu 2006	Duloxetine	153	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	80	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
STL-NY-94-	Van Ameringen	Sertraline	135	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	PCS score baseline	SD for PCS score baseline	PCS score mean change	SD for PCS score mean change	MCS score baseline	SD for MCS score baseline	MCS score mean change	SD for MCS score mean change
004	2001											
		Placebo	69	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Note: MCS: mental component score; PCS: physical component score; SD: standard deviation; SE: standard error; N/A: not available

Table 4b: Complete results available on EQ-5Djournal publications (received from industry or searched using ID from GSK on their website)

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	VAS baseline	SE for VAS baseline	EQ-5D VAS Change	EQ-5D SE for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
Protocol 648	Tucker 2001	Paroxetine	168	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	155	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Protocol 651	Marshall 2001	PAR 20mg	183	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		PAR 40mg	182	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	186	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	VAS baseline	SE for VAS baseline	EQ-5D VAS Change	EQ-5D SE for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
Protocol 651	Davidson 2001	Paroxetine	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Protocol 627	Stein 2003	Paroxetine	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Protocol 646	Stocchi 2003	Paroxetine	278	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	288	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Protocol 646	Stein 2001	Paroxetine	499	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	330	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Protocol 595	Stein 2002	Paroxetine	162	162	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	161	161	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Protocol 377	Berard 2006	Paroxetine	187	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	99	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Armstrong 2007	DLX 60mg QD	344	273	N/A	N/A	N/A	N/A	0.57	0.26 SE	0.2	0.01 SE
		DLX 60mg BD	341	255	N/A	N/A	N/A	N/A	0.56	0.26	0.02	0.01 SE
		Placebo	339	272	N/A	N/A	N/A	N/A	0.59	0.25	0.1	0.01 SE
HMAW-a	Fishbain 2006	DLX 60mg QD	344	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	VAS baseline	SE for VAS baseline	EQ-5D VAS Change	EQ-5D SE for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
		DLX 60mg BD	341	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	399	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Fishbain 2008	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Fishbain 2009	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Goldstein 2005	DLX 20mg	115	101	N/A	N/A	N/A	N/A	N/A	N/A	0.10	0.02
		DLX 60mg QD	114	104	N/A	N/A	N/A	N/A	N/A	N/A	0.13	0.02
		DLX 60mg BD	113	105	N/A	N/A	N/A	N/A	N/A	N/A	0.13	0.02 SE
HMAW-a	Goldstein 2005	Placebo	115	107	N/A	N/A	N/A	N/A	N/A	N/A	0.08	0.02 SE
HMAW-a	Guastella 2009	Duloxetine	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Hall 2010	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Pritchett 2007	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	VAS baseline	SE for VAS baseline	EQ-5D VAS Change	EQ-5D SE for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
HMAW-a	Wasan 2009	DLX 60mg QD	334	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 60mg BD	341	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Wernicke 2006	Duloxetine	222	204	N/A	N/A	N/A	N/A	0.8	0.2	0.0	0.01
		Placebo	115	107	N/A	N/A	N/A	N/A	0.7	0.2	-0.1	0.02
HMAW-a	Wernicke 2009	DLX 60mg QD	334	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		DLX 60mg BD	341	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Yuen 2014	Duloxetine	779	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Yuen 2014	Placebo	327	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Kajdasz 2007	Duloxetine	800	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	339	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HMAW-a	Wu 2006	Duloxetine	153	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	80	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
SBAMa	Cardozo 2004	Duloxetine	55	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	54	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Protocol	Publication	Intervention	Population in trial	Population for HRQoL at baseline	VAS baseline	SE for VAS baseline	EQ-5D VAS Change	EQ-5D SE for VAS change	utility baseline	SD for utility baseline	utility change	SD for utility change
STL-NY-94-004	Van Armeringen 2001	Sertraline	135	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
		Placebo	69	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Supplementary Document C: Correspondence with companies

The following are examples of correspondence with Eli Lilly, GSK and Pfizer from 16 April 2016 till 12 October 2016, done to get publications of the included trials and the missing data from the CSRs.

Letter 1: First letter of request sent to Eli Lilly and Company (14 April 2016)

Cochrane Nordic

Trusted evidence. Informed decisions. Better health.

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Eli Lilly Danmark A/S,
Lyskær 3E 2. tv,
DK-2730 Herlev,
Denmark

Dear Sir or Madam,

Subject: Application for access to all journal publications and quality of life data for the following placebo-controlled trials of duloxetine: protocols F1J-MC-HMAQa, F1J-MC-HMAQb, F1J-MC-HMAH, F1J-MC-HMBOa, F1J-MC-HMAWa, F1J-MC-SAAB, F1J-MC-SAAW and F1J-MC-SBAMa.

My colleagues and I at the Nordic Cochrane Centre are currently doing research on the effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on the quality of life of patients. The European Medicines Agency (EMA) has been most helpful in supplying us with PDF files of clinical study reports for these trials and we have undertaken literature searches in public databases to identify the corresponding journal publications.

However, we are uncertain whether we have captured all the journal articles for these trials, including secondary publications, from our searches and would therefore like to request all the journal publications for the following trials of duloxetine:

Protocol	Trial ID	Trial Title
a) F1J-MC-HMAQa	3327a	Duloxetine Versus Placebo in the Treatment of Major Depression
b) F1J-MC-HMAQb	3327b	Duloxetine Versus Placebo in the Treatment of Major Depression
c) F1J-MC-HMAH	1125	Duloxetine 20/30 mg vs. Placebo in Major Depression
d) F1J-MC-HMBOa	Not stated	Duloxetine versus Placebo in the Treatment of Fibromyalgia Patients with or without Major Depressive Disorder
e) F1J-MC-HMAWa	4098a	A Dose Response Study of Duloxetine versus Placebo in Patients with Painful Diabetic Neuropathy
f) F1J-MC-SAAB	1129	Duloxetine for Urinary Incontinence: A Multiple-Dose Study for Efficacy and Safety
g) F1J-MC-SAAW	1604	1604 Duloxetine Versus Placebo in the Relief of Stress Incontinence
h) F1J-MC-SBAMa	2624a	Efficacy and Safety of Duloxetine Compared with Placebo in Subjects Electing Surgery for Severe Pure Genuine Stress Incontinence

Additionally, the results of the quality of life questionnaires were missing from the reports we received for trials F1J-MC-HMAH (missing SF-36 results), F1J-MC-SAAB (missing SF-36 results), F1J-MC-SBAMa (missing EQ-5D both utility and VAS results) and F1J-MC-HMAWa (missing EQ-5D VAS results), so we would appreciate receiving those results from you.

Many thanks in advance. We look forward to hearing from you at your earliest convenience.

Kind regards,

Tarang Sharma – Researcher and PhD Fellow, Nordic Cochrane Centre, Denmark
Peter C. Gøtzsche – Professor and Director, Nordic Cochrane Centre, Denmark

Letter 2: First letter of request sent GlaxoSmithKline (14 April 2016)

Cochrane Nordic

Trusted evidence. Informed decisions. Better health.

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E-mail: ts@cochrane.dk
pcg@cochrane.dk

GlaxoSmithKline Pharma A/S
Nykær 68, Brøndby
DK-2605
Denmark

Dear Sir or Madam,

Subject: Application for access to all journal publications quality of life data for the following placebo-controlled trials of paroxetine: protocols 377, 595, 646, 648, 651 and 627.

My colleagues and I at the Nordic Cochrane Centre are currently doing research on the effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on the quality of life of patients. The European Medicines Agency (EMA) has been most helpful in supplying us with PDF files of clinical study reports for these trials and we have undertaken literature searches in public databases to identify the corresponding journal publications.

However, we are uncertain whether we have captured all the journal articles for these trials, including secondary publications, from our searches and would therefore like to request all the journal publications for the following trials of paroxetine:

Protocol	Trial Title
a) Protocol 377	A Double-blind, Multi-centre Placebo Controlled Study of Paroxetine in Adolescents with Unipolar Major Depression
b) Protocol 595	A Study of the Maintained Efficacy and Safety of Paroxetine versus Placebo in the Long-Term Treatment of Social Phobia
c) Protocol 646	A Study of the Maintained Efficacy and Safety of Paroxetine in Patients with Generalised Anxiety Disorder (GAD)
d) Protocol 648	A 12 Week, Double-blind, Placebo-controlled, parallel group study to assess the efficacy and tolerability of Paroxetine in Patients suffering from Posttraumatic Stress Disorder (PTSD)
e) Protocol 651	A 12 week, double-blind, fixed dose comparison of 20 and 40 mg daily of paroxetine and placebo in Patients suffering from Posttraumatic Stress Disorder (PTSD)
f) Protocol 627	A 12 week, double-blind, placebo-controlled, parallel group study to assess the efficacy and tolerability of paroxetine in patients suffering from Posttraumatic Stress Disorder (PTSD)

Additionally, the results of the quality of life questionnaires were missing from the reports we received for trials protocol 377 (missing EQ-5D utility results) and protocol 595 (missing EQ-5D VAS mean and standard error values, as only median and ranges are reported for double blind phase), so we would appreciate receiving those results from you.

Many thanks in advance. We look forward to hearing from you at your earliest convenience.

Kind regards,

Tarang Sharma – Researcher and PhD Fellow, Nordic Cochrane Centre, Denmark
Peter C. Gøtzsche – Professor and Director, Nordic Cochrane Centre, Denmark

Letter 3: First letter of request sent to Pfizer (14 April 2016)

Cochrane Nordic

Trusted evidence. Informed decisions. Better health.

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Rigshospitalet, Dept. 7811
Blegdamsvej 9
2100 Copenhagen Ø, Denmark
Tel: +45 35 45 71 12
Fax: +45 35 45 70 07
E-mail: ts@cochrane.dk
pcg@cochrane.dk

Pfizer Ballerup
Lautrupvang 8
2750 Ballerup, Denmark

Dear Sir or Madam,

Subject: Application for access to journal publications and quality of life data for the following placebo-controlled trials: protocols STL-NY-94-004 and 90CE21-0495 for sertraline and protocols 600A-302-US, CA, 600A-313-US, 0600B-209-US and 600A-303-US for venlafaxine (or venlafaxine extended release).

My colleagues and I at the Nordic Cochrane Centre are currently doing research on the effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on the quality of life of patients. The European Medicines Agency (EMA) has been most helpful in supplying us with PDF files of clinical study reports for these trials and we have undertaken literature searches in public databases to identify the corresponding journal publications.

However, we are uncertain whether we have captured all the journal articles for these trials, including secondary publications, from our searches. Additionally, the EQ-5D utility score results were missing from the reports we received for trial STL-NY-94-004 and so were the results of the quality of life questionnaire for trial 90CE21-0495 in its reports we received and it is unclear which instrument was employed for this trial.

Therefore we would like to request all the journal publications and the quality of life results for the following trials of sertraline:

Protocol	Trial Title
a) STL-NY-94-004	A twenty-week, prospective, randomized, multicenter, parallel group, double-blind, dose titration comparison of the safety, efficacy, and tolerability of sertraline (50-200 mg/day) and placebo in the treatment of DSM-IV generalized social phobia in outpatients
b) 90CE21-0495	Double-Blind Comparison of Sertraline, Clomipramine and Placebo in Outpatients with Obsessive Compulsive Disorder

The results of quality of life were also missing for some venlafaxine or venlafaxine extended release (ER) trials within the reports as it mentioned a special report for this outcome. We would therefore like to receive the quality of life results (special report on quality of life) and journal publications for the following trials of venlafaxine (or venlafaxine ER):

Protocol	Trial Title
a) 600A-302-US, CA	Randomized, double-blind comparison of venlafaxine (WY-45,030), trazodone, and placebo capsules in outpatients with major depression
b) 600A-313-US	Double-blind, placebo-controlled, parallel-group dosage-determination study of low doses of venlafaxine in depressed patients
c) 0600B-209-US	Double -blind, placebo-controlled study of venlafaxine ER in outpatients with major depression
d) 600A-303-US	Randomized, double-blind comparison of venlafaxine (WY-45,030), imipramine, and placebo capsules in outpatients with major depression

Many thanks in advance. We look forward to hearing from you at your earliest convenience.

Kind regards,

Tarang Sharma – Researcher and PhD Fellow, Nordic Cochrane Centre, Denmark
Peter C. Gøtzsche – Professor and Director, Nordic Cochrane Centre, Denmark

Letter 4: Second letter of request sent to GSK (10 July 2016)

Cochrane Nordic

Trusted evidence. Informed decisions. Better health.

Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
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Tel: +45 35 45 71 12
Fax: +45 35 45 70 07
E-mail: ts@cochrane.dk
pcg@cochrane.dk

GlaxoSmithKline Pharma A/S
Nykær 68, Brøndby
DK-2605
Denmark

Dear Sir or Madam,

Subject: Application for access to all journal publications quality of life data for the following placebo-controlled trials of paroxetine: protocols 377, 595, 646, 648, 651 and 627.

My colleagues and I at the Nordic Cochrane Centre are currently doing research on the effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on the quality of life of patients. The European Medicines Agency (EMA) has been most helpful in supplying us with PDF files of clinical study reports for these trials and we have undertaken literature searches in public databases to identify the corresponding journal publications.

However, we are uncertain whether we have captured all the journal articles for these trials, including secondary publications, from our searches and would therefore like to request all the journal publications for the following trials of paroxetine:

Protocol	Trial Title
a) Protocol 377	A Double-blind, Multi-centre Placebo Controlled Study of Paroxetine in Adolescents with Unipolar Major Depression
b) Protocol 595	A Study of the Maintained Efficacy and Safety of Paroxetine versus Placebo in the Long-Term Treatment of Social Phobia
c) Protocol 646	A Study of the Maintained Efficacy and Safety of Paroxetine in Patients with Generalised Anxiety Disorder (GAD)
d) Protocol 648	A 12 Week, Double-blind, Placebo-controlled, parallel group study to assess the efficacy and tolerability of Paroxetine in Patients suffering from Posttraumatic Stress Disorder (PTSD)
e) Protocol 651	A 12 week, double-blind, fixed dose comparison of 20 and 40 mg daily of paroxetine and placebo in Patients suffering from Posttraumatic Stress Disorder (PTSD)
f) Protocol 627	A 12 week, double-blind, placebo-controlled, parallel group study to assess the efficacy and tolerability of paroxetine in patients suffering from Posttraumatic Stress Disorder (PTSD)

Additionally, the results of the quality of life questionnaires were missing from the reports we received for trials protocol 377 (missing EQ-5D utility results) and protocol 595 (missing EQ-5D VAS mean and standard error values, as only median and ranges are reported for double blind phase), so we would appreciate receiving those results from you.

Many thanks in advance. We look forward to hearing from you at your earliest convenience.

Kind regards,

Kristine Rasmussen – Researcher, Nordic Cochrane Centre, Denmark
Tarang Sharma – Researcher and PhD Fellow, Nordic Cochrane Centre, Denmark
Peter C. Gøtzsche – Professor and Director, Nordic Cochrane Centre, Denmark

Letter 5: Second letter of request sent to Pfizer (25 May 2016)

Fwd: study protocols sertaline and venlafaxine - Pfizer

tarang sharma <ts@cochrane.dk> 25. maj 2016 kl. 10.23
Til: "van Lith, Rob" <Rob.vanLith@pfizer.com>
Cc: Kristine Rasmussen <kristinersmssn@gmail.com>, Peter Gøtzsche <pcg@cochrane.dk>

Dear Rob,

Many thanks for your response and trying to find the data we requested within your databases, though it appears you have not been able to identify it.

To answer your specific questions: I'm a Research and PhD fellow with the Nordic Cochrane Centre and the University of Copenhagen studying the quality of life of patients on antidepressants and the adverse effects of these drugs. We have received the protocol numbers and the clinical study reports (CSRs) from the European Medicines Agency (EMA) for our research project.

However, as mentioned in my previous letter of request, some quality of life results information were missing from the CSRs we received from the regulator:
"the EQ-5D utility score results were missing from the reports we received for trial STL-NY-94-004 and so were the results of the quality of life questionnaire for trial 90CE21-0495 in its reports we received and it is unclear which instrument was employed for this trial."
"The results of quality of life were also missing for some venlafaxine or venlafaxine extended release (ER) trials within the reports as it mentioned a special report for this outcome. We would therefore like to receive the quality of life results (special report on quality of life) for the trials, 600A-302-US, CA, 600A-313-US, 0600B-209-US and 600A-303-US."

Our aim is to also compare the data with that available from the published journal articles, so therefore have also requested all journal publications for the trials: protocols STL-NY-94-004 and 90CE21-0495 for sertraline and protocols 600A-302-US, CA, 600A-313-US, 0600B-209-US and 600A-303-US for venlafaxine (or venlafaxine extended release).

Hope this will help you identify the data we are looking for. Many thanks again for helping us with this request.

Kind regards,
Tarang

Letter 6: Third letter of request sent to Pfizer (11 July 2016)

Cochrane Nordic

Trusted evidence. Informed decisions. Better health.

Nordic Cochrane Centre
Rigshospitalet, Dept. 7811
Blegdamsvej 9
2100 Copenhagen Ø, Denmark
Tel: +45 35 45 71 12
Fax: +45 35 45 70 07
E-mail: ts@cochrane.dk
pcg@cochrane.dk

Pfizer Ballerup
Lautrupvang 8
2750 Ballerup, Denmark

Dear Sir or Madam,

Subject: Application for access to journal publications and quality of life data for the following placebo-controlled trials: protocols STL-NY-94-004 and 90CE21-0495 for sertraline and protocols 600A-302-US, CA, 600A-313-US, 0600B-209-US and 600A-303-US for venlafaxine (or venlafaxine extended release).

My colleagues and I at the Nordic Cochrane Centre are currently doing research on the effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on the quality of life of patients. The European Medicines Agency (EMA) has been most helpful in supplying us with PDF files of clinical study reports for these trials and we have undertaken literature searches in public databases to identify the corresponding journal publications.

However, we are uncertain whether we have captured all the journal articles for these trials, including secondary publications, from our searches. Additionally, the EQ-5D utility score results were missing from the reports we received for trial STL-NY-94-004 and so were the results of the quality of life questionnaire for trial 90CE21-0495 in its reports we received and it is unclear which instrument was employed for this trial.

Therefore we would like to request all the journal publications and the quality of life results for the following trials of sertraline:

Protocol	Trial Title
a) STL-NY-94-004	A twenty-week, prospective, randomized, multicenter, parallel group, double-blind, dose titration comparison of the safety, efficacy, and tolerability of sertraline (50-200 mg/day) and placebo in the treatment of DSM-IV generalized social phobia in outpatients
b) 90CE21-0495	Double-Blind Comparison of Sertraline, Clomipramine and Placebo in Outpatients with Obsessive Compulsive Disorder

The results of quality of life were also missing for some venlafaxine or venlafaxine extended release (ER) trials within the reports as it mentioned a special report for this outcome. We would therefore like to receive the quality of life results (special report on quality of life) and journal publications for the following trials of venlafaxine (or venlafaxine ER):

Protocol	Trial Title
a) 600A-302-US, CA	Randomized, double-blind comparison of venlafaxine (WY-45,030), trazodone, and placebo capsules in outpatients with major depression
b) 600A-313-US	Double-blind, placebo-controlled, parallel-group dosage-determination study of low doses of venlafaxine in depressed patients
c) 0600B-209-US	Double -blind, placebo-controlled study of venlafaxine ER in outpatients with major depression
d) 600A-303-US	Randomized, double-blind comparison of venlafaxine (WY-45,030), imipramine, and placebo capsules in outpatients with major depression

Many thanks in advance. We look forward to hearing from you at your earliest convenience.

Kind regards,
Kristine Rasmussen – Researcher, Nordic Cochrane Centre, Denmark
Tarang Sharma – Researcher and PhD Fellow, Nordic Cochrane Centre, Denmark
Peter C. Gøtzsche – Professor and Director, Nordic Cochrane Centre, Denmark

Letter 7: Third letter of request sent to Pfizer (14 September 2016)

Request for data and publications

Kristine Rasmussen <kristinersmssn@gmail.com> 14. september 2016 kl. 08.45
Til: medical.information@pfizer.com
Cc: Peter Gøtzsche <pcg@cochrane.dk>, tarang sharma <ts@cochrane.dk>, asp@cochrane.dk

Dear Henrik Jørgensen,

We are sorry to hear that you are unable to facilitate our request regarding protocols STL-NY-94-004 and 90CE21-0495 for sertraline and protocols 600A-302-US, CA, 600A-313-US, 0600B-209-US and 600A-303-US for venlafaxine (or venlafaxine extended release).

We are grateful for your willingness to conduct literature searches relating to your products, and would like to receive any publications relating to protocols STL-NY-94-004 and 90CE21-0495 for sertraline and protocols 600A-302-US, CA, 600A-313-US, 0600B-209-US and 600A-303-US for venlafaxine (or venlafaxine extended release). However, these will not be sufficient for our research.

Specifically, we are requesting all information on quality of life as mentioned in protocols STL-NY-94-004 and 90CE21-0495 for sertraline and protocols 600A-302-US, CA, 600A-313-US, 0600B-209-US and 600A-303-US for venlafaxine (or venlafaxine extended release), please see attached for further details.

The Cochrane Collaboration is a leading global organization with an emphasis on evidence-based medicine and our work informs healthcare and drug policy in countries around the world. We believe drug companies have a moral obligation towards the patients who volunteer for the trials and society at large to provide all information related to clinical trials on their drugs, enabling independent research to be carried out. In relation to our specific research project, many of Pfizer's competitors have been forthcoming with providing unpublished data and publications relating to their products and we hope that you will reconsider your decision to withhold the data that we need for our research.

We wish to remind Pfizer that the EU ombudsman ruled in 2010 that there is no commercially confidential information in clinical study reports and trial reports.[1] If you feel unable to assist us, then please ask your superiors to do so.

Kind regards,

Kristine

Kristine Rasmussen
Researcher
Cochrane
Nordic
Nordic Cochrane Centre, Rigshospitalet Dept. 7811, Blegdamsvej 9,
2100 Ø Copenhagen, Denmark

[1] Gøtzsche PC, Jørgensen AW. Opening up data at the European Medicines Agency. BMJ 2011; 342: d2686.

Letter 8: First letter received from Eli Lilly and Company (26 April 2016)

Medical Information

Eli Lilly Danmark A/S
Lyskær 3E, 2tv.
DK - 2730 Herlev
Telefon: +45 45 26 61 00
scan_medinfo@lilly.com
www.eli-lilly.dk

26 April 2016
ID-nr: 0395950

Dear Tarang Sharma,

Thank you for your request for medical information regarding CYMBALTA and data/publications.

In the enclosed material you will find available information related to your request. The answer may contain off label information. Please see local label for approved indication.

The information is intended only as a scientific exchange in response to a specific unsolicited request and should not been seen as a treatment recommendation from Lilly.

We hope that the enclosed information will respond to your enquiry. Should you require any further assistance, please do not hesitate to contact us again, please see contact details below.

Best regards,

Eli Lilly Medical Information

Letter 9: Second letter received from Eli Lilly and Company (28 April 2016)

Medical Information

Eli Lilly Danmark A/S
Lyskær 3E, 2tv.
DK - 2730 Herlev
Telefon: +45 45 26 61 00
scan_medinfo@lilly.com
www.eli-lilly.dk

28 April 2016
ID-nr: 0396576

Dear Tarang Sharma,

Thank you for your request for medical information regarding CYMBALTA and studies.

In the enclosed material you will find available information related to your request. The answer may contain off label information. Please see local label for approved indication.

The information is intended only as a scientific exchange in response to a specific unsolicited request and should not been seen as a treatment recommendation from Lilly.

We hope that the enclosed information will respond to your enquiry. Should you require any further assistance, please do not hesitate to contact us again, please see contact details below.

Best regards,

Eli Lilly Medical Information

Letter 10: First letter part 1 received from GSK (20 July 2016)

RE: Request for additional data and publications for trials of paroxetine

Nordic MedInfo <nordic.medinfo@gsk.com> 13. juli 2016 kl. 08.53
Til: "kristinersmssn@gmail.com" <kristinersmssn@gmail.com>

Dear Kristine,

Thank you for your enquiry regarding additional data and publications for trials of paroxetine.

You will shortly receive a response to your question in a separate e-mail from GSK's Global Medical Information Database.

Please use the link in the response and enter GSK ID (29060/protocol number)

I hope this response answers your question. If you require any further information please contact me directly.

Kind regards,

Christina Dyg, M.Sc.

Nordic Medical Information Hub

Medical Information Specialist

GSK

Nykær 68, DK-2605 Brøndby, Denmark

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gsk.com | Twitter | YouTube | Facebook | Flickr

Letter 11: First letter part 2 received from GSK (20 July 2016)

Svar på henvendelse om: Seroxat,: 13910356

Medical Information <rd.wisdom_production@gsk.com> 13. juli 2016 kl. 08.54
Til: kristinersmssn@gmail.com

Kære Kristine Rasmussen,

Tak for din henvendelse til GlaxoSmithKline (GSK).

Du spurgte om: Request for additional data and publications for trials of paroxetine:

Som svar modtager du vedhæftede information:
- Data on File for Paroxetine Tablets Available on Clinical Trial Register

Materialet du modtager er fra GSK's Global Medical Information. Med denne service sikrer vi, at svar på henvendelser om vores lægemidler er gennemarbejdet af specialister inden for det givne terapeutiske område.

Det tilsendte materiale er i Adobe Acrobat format og er kun til brug for besvarelse af det konkrete spørgsmål. Adobe Acrobat kan hentes gratis på http://ww38.adope.com. Materialet eller dele af dette må ikke reproduceres eller kopieres.

Supplerende henvises til det lokale godkendte produktresumé på http://www.produktresume.dk

Hvis du har spørgsmål til ovenstående, eller du har brug for yderligere information, er du velkommen til at kontakte Medicinsk Information på nordic.medinfo@gsk.com eller telefon nr. 3635 9100.

Bemærk at denne e-mail ikke kan besvares – skriv i stedet til nordic.medinfo@gsk.com

Undersøgelse:GSK Medicinsk Information sætter stor pris på din feedback for at sikre, at vores service opfylder dine behov på bedste vis. Venligst klik på følgende link for at udfylde en kort spørgeundersøgelse. Spørgeundersøgelsen tager ca. 2 minutter http://survey.gsk.com/TakeSurvey.aspx?SurveyID=n23ImnlK

Med venlig hilsen
Christina Dyg
Nordic Medical Information Hub
GlaxoSmithKline AS

Danmark

13910356

Letter 12: First letter part 3 received from GSK (20 July 2016)

Data on File for *Paroxetine* Available on Clinical Trial Register

The data on file reference you requested is publicly available on the GlaxoSmithKline Clinical Study Register which is accessible via the following link:

http://www.gsk-clinicalstudyregister.com/.

Letter 13: First letter received from Pfizer (17 May 2016)

On Tue, May 17, 2016 at 1:12 PM, van Lith, Rob <Rob.vanLith@pfizer.com> wrote:

> Dear Tarang,
>
> Thank you for contacting us regarding your question on our products sertraline and venlafaxine.
>
> You requested to receive some additional data and publications for sertraline and venlafaxine, and mentioned some specific protocol names. We have searched our database, but unfortunately, this did not immediately lead to the specific items you mentioned. To understand your question better and to aim for the right information, we would like to receive some additional information from you. Could you possibly clarify what the exact reason is that you need further information on this topic, and where you did find the protocol numbers you mentioned? And what type of information on the QoL in patients using sertraline and venlafaxine do you exactly need?
>
> To help you obtain the right information, based on your input we will then create some specific documents on the quality of life in patients using sertraline or venlafaxine.

ps://mail.google.com/mail/u/0/?ui=2&ik=28e8f6e41c&view=pt&q=pfizer&qs=true&search=query&msg=154e7028d48320f7&siml=154e7028d48320f7

> Many thanks in advance,
>
> Rob
>
> **Rob van Lith, MSc**
> Medical Information Specialist - *Neuroscience & Pain*
> Country Relationship Manager Belgium, Netherlands & Luxembourg
> Pfizer Medical Information - Europe, Middle East & Africa (EMEA)
>
> Customers: Connect to Pfizer Medical Information online & by telephone

Letter 14: Second letter received from Pfizer (18 July 2016)

Pfizer Medical Information
E-Mail: EUMedInfo@Pfizer.com

Ms. Kristine Rasmussen
Nordic Cochrane Centre
Rigshospitalet Dept. 7811
Blegdamsvej 9
København Ø, 2100

18 July 2016

Your medical information enquiry concerning ZOLOFT (sertraline HCl) and EFEXOR (venlafaxine)

Dear Ms. Rasmussen,

Thank you for your enquiry regarding our medicines Zoloft and Efexor, you requested additional publication information on trials for venlafaxine and sertraline.

Pfizer cannot send any study protocols or internal data for the trials requested since this is proprietary information. If you wish, Medical Information can conduct a search and send a citation listing with published studies on "Effects on Quality of Life" for both venlafaxine and sertraline.

I hope this information proves to be of help and interest. Please do not hesitate to contact us if you require anything further.

Yours sincerely

Henrik Jorgensen
Medical Information Associate

Ref: DK16-000434

Disclaimers
Pfizer stores your personal information to enable us to address your enquiry, complaint or other matters that you have raised, and to document our response. Your information will only be used for this purpose, unless required for legal proceedings. If reporting an adverse event, the information provided will be used in order to meet our regulatory requirements relating to the safety of our medicines. It may be necessary to share your personal information with Pfizer affiliates, partners and regulatory authorities located both within and outside of your home country. In accordance with applicable law, you may have a right to access and correct your information. For any question regarding our use of your personal information please contact us by using the local Pfizer telephone number, or by e-mail: EUMedInfo@Pfizer.com

Letter 15: Third letter received from Pfizer (12 October 2016)

Pfizer Medical Information
E-Mail: EUMedInfo@Pfizer.com

Ms. Kristine Rasmussen
Nordic Cochrane Centre
Rigshospitalet Dept. 7811
Blegdamsvej 9
København Ø, 2100

12 October 2016

Your medical information enquiry concerning EFEXOR DEPOT (venlafaxine) and ZOLOFT (sertraline)

Dear Ms. Rasmussen,

Thank you for your enquiry regarding our medicines Efexor Depot and Zoloft, you requested information on quality of life trial data for Zoloft (sertraline) and Efexor (venlafaxine).

We thank you for your feedback. You query has been investigated into and we are now able to provide you with the following information:

To access patient-level data, researchers should submit a research proposal. An internal committee composed of Pfizer colleagues who are familiar with the data, reviews all in-scope applications. If the application is denied or only partially approved, an Independent Review Panel of outside experts will review the application. The Independent Review Panel's decision is considered final and binding. For further instructions please use the following link:

http://www.pfizer.com/research/clinical_trials/trial_data_and_results/data_requests

I hope this information proves to be of help and interest. Please do not hesitate to contact us if you require anything further.

Yours sincerely

Henrik Jørgensen
Medical Information Associate

Ref: DK16-000580

Disclaimers
Pfizer stores your personal information to enable us to address your enquiry, complaint or other matters that you have raised, and to document our response. Your information will only be used for this purpose, unless required for legal proceedings. If reporting an adverse event, the information provided will be used in order to meet our regulatory requirements relating to the safety of our medicines. It may be necessary to share your personal information with Pfizer affiliates, partners and

Statement from co-authors

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

DECLARATION OF CO-AUTHORSHIP

Information on PhD student:	
Name of PhD student	Tarang Sharma
E-mail	tarangs@gmail.com
Date of birth	29/10/1979
Work place	Nordic Cochrane Centre
Principal supervisor	Peter C. Gøtzsche

Title of PhD thesis:
Effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on suicidality, violence, and quality of life.

This declaration concerns the following article:
Sharma T, Guski LS, Freund N, Gøtzsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. BMJ 2016; 352:i65.

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	B
4. Presentation, interpretation and discussion in a journal article format of obtained data	B

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

Signature of the co-authors:			
Date:	Name:	Title:	Signature:
24/1-18	Louise Schow Guski	MD	Louise Schow Guski
26/1-18	Nanna Freund	MD	Nanna Freund

Signature of the PhD student and the principal supervisor:	
Date: 4/12/2017	Date: 4 Dec 17
PhD student:	Principal supervisor:

DECLARATION OF CO-AUTHORSHIP

Information on PhD student:	
Name of PhD student	Tarang Sharma
E-mail	tarangs@gmail.com
Date of birth	29/10/1979
Work place	The Nordic Cochrane Centre
Principal supervisor	Peter C. Gøtzsche

Title of PhD thesis:
Effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on suicidality, violence, and quality of life.

This declaration concerns the following article:
SharmaT, Gøtzsche PC, Kuss O. The Yusuf-Peto method was not a robust method for meta-anlayses of rare events data from antidepressant trials. Journal of Clinical Epidemiology, 2017 Nov;91:129-136.

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	C
2. Planning of the experiments and methodology design, including selection of methods and method development	B
3. Involvement in the experimental work	B
4. Presentation, interpretation and discussion in a journal article format of obtained data	B

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

Signature of the co-authors:			
Date:	Name:	Title:	Signature:
4.12.17	Oliver Kuss	Professor	

Signature of the PhD student and the principal supervisor:	
Date: 4/12/2017 PhD student:	Date: 4 Dec 17 Principal supervisor:

DECLARATION OF CO-AUTHORSHIP

Information on PhD student:	
Name of PhD student	Tarang Sharma
E-mail	tarangs@gmail.com
Date of birth	29/10/1979
Work place	Nordic Cochrane Centre
Principal supervisor	Peter C. Gøtzsche

Title of PhD thesis:
Effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on suicidality, violence, and quality of life.

This declaration concerns the following article:
Sharma T, Guski LS, Freund N, Meng DD, Gøtzsche PC. Drop-outs rates in placebo-controlled trials of antidepressant drugs: systematic review and meta-analysis based on clinical study reports. (Submitted to BMJ)

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	B
4. Presentation, interpretation and discussion in a journal article format of obtained data	B

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

Signature of the co-authors:			
Date:	Name:	Title:	Signature:
24/1-18	Louise Schow Guski	MD	
26/1-18	Nanna Freund	MD	
	Dina Muscat-Meng	Mrs	

Signature of the PhD student and the principal supervisor:	
Date: 4/12/2017 PhD student:	Date: 4 Dec 17 Principal supervisor:

GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

DECLARATION OF CO-AUTHORSHIP

Information on PhD student:	
Name of PhD student	Tarang Sharma
E-mail	tarangs@gmail.com
Date of birth	29/10/1979
Work place	Nordic Cochrane Centre
Principal supervisor	Peter C. Gøtzsche

Title of PhD thesis:

Effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on suicidality, violence, and quality of life.

This declaration concerns the following article:

Sharma T, Guski LS, Freund N, Meng DD, Gøtzsche PC. Drop-outs rates in placebo-controlled trials of antidepressant drugs: systematic review and meta-analysis based on clinical study reports. (Submitted to BMJ)

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	B
4. Presentation, interpretation and discussion in a journal article format of obtained data	B

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

Signature of the co-authors:

Date:	Name:	Title:	Signature:
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	Nanna Freund	MD	
25/1/18	Dina Muscat-Meng	Mrs	

Signature of the PhD student and the principal supervisor:

Date: 4/12/2017	Date: 4 Dec 17
PhD student:	Principal supervisor:

DECLARATION OF CO-AUTHORSHIP

Information on PhD student:	
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Effects of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) on suicidality, violence, and quality of life.

This declaration concerns the following article:

Sharma T, Rasmussen K, Paludan-Müller A, Gøtzsche PC. Selective reporting of SF-36 and EQ-5D health related quality of life outcomes in clinical study reports and publications of antidepressant trials. (Draft manuscript)

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
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3. Involvement in the experimental work	B
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Date: 30-01-2018	Date: 29-1-18
PhD student:	Principal supervisor:

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Best wishes,

Laura

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Title: The Yusuf-Peto method was not a robust method for meta-analyses of rare events data from antidepressant trials

Author: Tarang Sharma,Peter C. Gøtzsche,Oliver Kuss

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