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Differences in Reporting Serious Adverse Events in Industry Sponsored Clinical Trial Registries and Journal Articles on Antidepressant and Antipsychotic Drugs - A Cross-sectional Study

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ABSTRACT

Objective: To examine the degree of concordance in reporting serious adverse events (SAEs) from psychotropic drug trials among journal articles and clinical trial summaries, and to categorize types of discrepancies.

Design: Cross-sectional study of summaries of all antidepressant and antipsychotic trials included in an online trial registry and their first associated stand-alone journal articles.

Setting: Clinicalstudyresults.org, sponsored by Pharmaceutical Research and Manufacturers of America; clinicaltrials.gov, administered by the US National Institutes of Health.

Main outcome measure: Three coders extracted data on the numbers and types of SAEs.

Results: 244 trial summaries for six antidepressant and antipsychotic drugs were retrieved, 142 (58.2%) listing an associated article. Of 1,608 SAEs in drug-treated participants according to trial summaries, 694 (43.2%) did not appear in associated articles. Nearly 60% of SAEs counted in articles and 41% in trial summaries had no description. Most cases of death (62.3%) and suicide (53.3%) were not reported in articles. Half or more of the 142 pairs were discordant in reporting the number (49.3%) or description (67.6%) of SAEs. These discrepancies resulted from journal articles' 1) omission of complete SAE data, 2) reporting acute phase study results only, and 3) more restrictive reporting criteria. Trial summaries with zero SAE were 2.35 (95% confidence interval, 1.58 to 3.49; P<0.001) times more likely to be published with no discrepancy in their associated journal article. Since clinicalstudyresults.org was removed from the Internet in 2011, only 7.8% of retrieved trial summaries appear with results on clinicaltrials.gov.

Conclusions: Substantial discrepancies exist in SAE data found in journal articles and registered summaries of antidepressant and antipsychotic drug trials. The two main scientific sources accessible to clinicians and researchers are limited by incomplete, ambiguous, and inconsistent reporting. Access to complete and accurate data from clinical trials of drugs currently in use remains a pressing concern.

ARTICLE SUMMARY

Strengths and limitations of this study

- Published journal articles from antidepressant and antipsychotic drug trials report substantially fewer serious adverse events than associated clinical trial summaries posted by industry trial sponsors on a previously active online registry.
- Our findings of inconsistencies and ambiguities in serious adverse event reporting in both journal articles and trial summaries suggest that information in registries might not provide meaningfully improved access to complete and transparent clinical trial data.
- The registry from which we retrieved trial summaries has since been removed from the Internet and most trial summaries were not transferred with results to clinicaltrials.gov, making our analysis a unique examination of data that has been lost or scattered.
- We examined only the first stand-alone journal article associated with each trial summary, so it is possible that additional harms outcomes and longer-term outcomes absent from our sample of journal articles were reported in subsequent articles. Nevertheless, clear trends of incomplete reporting were apparent between journal article and trial summary sources.

INTRODUCTION

Publication bias and concerns regarding the integrity of the medical treatment knowledge base have led to various mechanisms, such as publicly accessible clinical trial registries, to promote transparent and complete reporting of clinical trial results [1, 2]. As the next most accessible source of drug information after published articles, clinical trial summaries available in online trial registries might contribute to improved evidence synthesis since they are supposed to provide an inclusive synopsis of both positive and negative results [3, 4]. In this study we compare serious adverse events (SAEs) found in industry-funded antipsychotic and antidepressant drug trial summaries posted by trial sponsors on an online trial registry, with SAEs found in published journal articles reporting on the same trials.

SAEs by definition result in death, hospitalization or significant disability and are therefore particularly important to report from a clinical trial because of their potential impacts on treatment decision-making and patient safety. International Conference on Harmonization (ICH) guidelines state that SAEs "deserve special attention" relative to other types of adverse effects, including providing individual-level patient detail and narrative for each SAE in clinical trial reports submitted to regulatory agencies [5]. Regulatory agencies in the United States and across Europe require trial sponsors to immediately report unexpected or life-threatening SAEs [6, 7]. However, the extent to which SAEs are then reported in outlets for clinicians, researchers, and the public is unknown, though evidence suggests incomplete and ambiguous reporting of harms-related data [8-10]. Recent settlements resulting from state and federal lawsuits in the United States against pharmaceutical manufacturers for minimizing or concealing drug harms, further highlight the need for increased diligence in discerning what important harm-related drug

information might remain unknown or distorted in scientific outlets for reporting clinical trial results [11-13].

Antipsychotic and antidepressant drugs — which rank among the 10 highest-selling drug classes in the U.S. and the world [14, 15] — are mainstay treatments in psychiatry and prescribed for myriad indicated and off-label, psychiatric and non-psychiatric uses [16, 17]. Journal publications and clinical trial summaries posted on trial registries currently represent the primary information sources for clinicians and decision-makers regarding the safety and effectiveness of drug treatments. In contrast to substantially lengthier accounts of trials found in clinical study reports submitted to regulatory agencies, clinical trial summaries are abbreviated, concise descriptions of trials' background, methodology, and positive and negative results and, similar to clinical study reports, prepared according to templates described in the ICH *Guidelines for Industry: Structure and Content of Clinical Study Reports* [5]. Using the clinical trial summaries for all trials of these drugs posted by industry sponsors on clinicalstudyresults.org, we aimed to 1) count and describe SAEs reported in trial summaries and, as applicable, their associated peer-reviewed journal articles, 2) assess the consistency of SAE reporting between pairs of trial summaries and associated journal articles, and 3) categorize possible explanations for discrepant reporting.

METHODS

Data Sources

Clinical trials summaries were retrieved from clinicalstudyresults.org, the former online public registry sponsored by the Pharmaceutical Research and Manufacturers of America (PhRMA). Published journal articles were identified using the bibliography listed on the cover page of each trial summary.

2.1.1 Clinical trial summaries

The clinicalstudyresults.org registry was established in 2005 by PhRMA as a single repository for pharmaceutical manufacturers to post result summaries of their sponsored clinical trials. At the time, the federally funded clinicaltrials.gov, established in 2000 and administered by the U.S. National Institutes of Health, required manufacturers to register only the existence of their trials. According to PhRMA guidelines, complete results of all hypothesis-testing clinical trials completed after 2002 for products approved for marketing in the United States were to be submitted to its registry within one year after completion of the trial, and references to articles published in peer-reviewed journals added to the trial summary as soon as they were published [18].

In May 2011, we retrieved all Phase II, III, and IV clinical trial summaries (n=329) for all nine drugs within the antidepressant and antipsychotic classes listed on clinicalstudyresults.org. We excluded three drugs (desvenlafaxine, quetiapine, and venlafaxine) with registered trials but no or few posted trial summaries. For the remaining six drugs (n=254 trial summaries) we retained the summaries with trial completion dates on or before 2008, allowing at least 2.5 years for a trial to reach publication in the peer-reviewed literature (see Appendix Table 1). This resulted in 244 (74%) clinical trial summaries for six drugs from three manufacturers: aripiprazole (Abilify, Bristol-Myers Squibb), atomoxetine (Strattera, Eli Lilly), duloxetine (Cymbalta, Eli Lilly), olanzapine (Zyprexa, Eli Lilly), sertraline (Zoloft, Pfizer), and ziprasidone (Geodon, Pfizer). Trial summaries averaged 18 pages in length (range: 3 to 147). Supplementary File 1 provides a trial summary illustrating the typical format of the documents in this sample. Trial summaries include both pre-marketing studies that were sent to regulatory

agencies for drug approval and post-marketing studies for new indications, additional outcomes, and long-term follow-up.

Journal articles

Using the bibliography listed on the cover page of each trial summary, we counted a total of 496 listed publications (an average of two publications per trial, with an average time to publication of 2.5 years), from which we retrieved the earliest journal article reporting on the full trial. From the total we excluded 261 (52.6%) sub-set analyses (i.e., reports on a sub-set of the total sample based on a shared characteristic, such as gender), meta-analyses, and conference abstracts. Of the 244 trial summaries, 142 (58.2%) listed an associated stand-alone journal article. We emailed and telephoned the medical communications, clinical trials, or customer relations department of each manufacturer of the included drugs to inquire about the completeness of the list of trial summaries and journal articles posted on clinicalstudyresults.org. No representative from any manufacturer could confirm completeness of the posted lists nor provide a current list of all clinical trials and journal publications for the respective drugs. Representatives directed us to visit clinicaltrials.gov to view current and completed trials, and PubMed for a list of publications. We then attempted to manually search PubMed to match possible additional publications with the trial summaries, but the absence of trial identification numbers in journal articles made it extremely difficult to crosscheck and match all sources reliably. These additional efforts, therefore, did not affect the final sample size, which consisted of 142 trial summary-journal article pairs listed on clinicalstudyresults.org and an additional 102 trial summaries from the registry with no associated journal article (see Figure 1).

Data Extraction

We employed double data extraction. One coder extracted the number and exact description of SAEs reported to occur in drug-treated participants from the *Results* section of each of the 244 trial summaries and 142 journal articles. For multi-phase trials, we tallied the SAEs occurring in each phase. The number of patients experiencing SAEs was counted in the few cases where the number of events was not provided, therefore underestimating the actual number of SAEs. We also extracted from each source the trial start and completion year, article publication date, study length, sample size, targeted indication, and consistency of reporting SAEs (see explanation below). A second coder independently extracted these data from a 50% random sample of trial summaries and articles for three of the six drugs. A third coder repeated the same process for the other three drugs. The values obtained by the second and third coders were compared to those obtained by the first. Any discrepancies were resolved by consensus. Coding for most reports and articles was straightforward and few disagreements in recordings between coders were found.

We evaluated the consistency of the number and description of SAEs occurring in drug-treated participants reported between each trial summary and its associated article (142 pairs). The *number* of SAEs was considered inconsistent if (1) reported numbers differed between the two sources (e.g., aripiprazole trial CN138-008: trial summary cited 7, journal article 6, SAEs), (2) one source reported the number of SAEs while the other contained no or an ambiguous statement about their occurrence; or (3) the journal article did not report the trial phase in which SAEs did occur according to the trial summary (e.g., ziprasidone trial 1006: in a 60-week multi-phase study with 8 SAEs reported in the summary, the article reports findings from the 8-week acute phase with zero SAEs). The *description* of SAEs was considered inconsistent if only one source described the events (e.g., duloxetine trial 6091: the summary describes 1 SAE as an

intentional overdose, the article omits the description but accurately reports the number), or if one source less completely described the events than the other source (e.g., duloxetine trial 8601: the summary lists one death from suicide as well as other SAEs related to psychiatric worsening, but the article mentions only the suicide). Sources were considered consistent if both reported the number or description of SAEs identically, or if neither reported such information. In each instance of discrepant reporting, we carefully reviewed the trial summary and journal article to clarify the form of the inconsistency and then categorized our findings.

Analysis

We used descriptive statistics to summarize quantitative variables related to study characteristics and frequencies for categorical variables. We calculated the number of SAEs per patient treated for each drug by dividing the number of SAEs reported in trial summaries and journal articles, respectively, by the total number of drug-treated participants.

We extracted exact descriptions of SAEs and then categorized them as: behavioral or cognitive, physical, no description provided, and unspecified (including overdose, dependence, death or hospitalization for unspecified reasons, and accidental injury). We further counted the number of SAEs reported as death, suicide, suicide attempt, homicidal ideation, and new or worsened psychiatric symptoms.

We calculated risk ratios to test the likelihood of trial summaries reporting zero SAEs to be published as stand-alone journal articles in a manner congruent with the summaries, compared to trial summaries reporting ≥ 1 SAEs. Risk ratios were calculated with 95% confidence intervals and Pearson's chi-square analysis using PASW Statistics, version 18 software [19].

RESULTS

Sample Description

For each of the six drugs included in this analysis, Table 1 summarizes trial characteristics as reported in trial summaries, their associated journal articles, and the additional trial summaries having no associated journal article (referred to as *unpublished trial summary* on all tables and appendices). Journal articles reported findings for an identical or nearly identical number of participants as their associated trial summaries. The 102 unpublished summaries, however, included data on an additional 20,084 drug-treated participants. The median study length was shorter in journal articles (11 weeks) than in their paired trial summaries (12 weeks) or unpublished trial summaries (16 weeks).

The three antipsychotic drugs (n=129 trial summaries) were being tested for the treatment of psychotic disorders (56.6% of studies), bipolar disorder or mania (26.4%), or other conditions (16.2%) such as depressive disorders, Alzheimer's, autism, alcohol dependence, or borderline personality disorder. The three antidepressant drugs (n=115 trial summaries) were being studied for the treatment of attention deficit hyperactivity disorder (42.6%), depressive disorders (34.8%), anxiety disorders (8.7%), or other conditions (14%) such as pain-related disorders or post-traumatic stress disorder.

Serious Adverse Events in Trial Summaries

Ninety percent of all trial summaries (n=244) reported a precise number of SAEs occurring in the trial. The 142 trial summaries with an associated journal article reported 1,608 SAEs, and the 102 trial summaries with no associated journal article reported an additional 1,423 SAEs. Table 2 details the total and per patient numbers of SAEs reported in trial summaries for each drug. Appendix Table 2 lists additional SAEs for the 10 excluded trial summaries with trial completion dates in 2009 or later.

No description was provided for 41% of the SAEs cited in trial summaries (46% and 20% of SAEs in antipsychotic and antidepressant trials, respectively). An additional 11.6% of SAEs were non-specifically described, such as "accidental injury" in duloxetine trial 1126. When a specific description was present, we categorized 28.4% of SAEs as behavioral or cognitive and 18.9% as physical. Table 3 details all cases of death, suicide, and new or worsened psychiatric symptoms for each drug.

Serious Adverse Events in Journal Articles

Nearly 40% of journal articles failed to specify the number of SAEs that occurred in the trial (Table 2), containing either no statement related to SAEs or an ambiguous statement without an actual number of SAEs, such as sertraline trial 1060: "no subjects had serious adverse events related to study treatment." A total of 914 SAEs were reported across the 85 journal articles that did include specific data on SAE occurrence.

Most SAEs (58.9%) reported in journal articles (61% in antipsychotic and 55.5% in antidepressant trials) had no accompanying description and another 8% were non-specifically described. Nearly one-fifth (18.9%) of SAEs were behavioral or cognitive in nature and 14.6% were described as physical. Table 3 shows that one-quarter of SAEs described in journal articles were categorized as death, suicide, homicidal ideation, or new or worsened psychiatric symptoms.

Consistency of Reporting in Trial Summary-Journal Article Pairs

Just over half (56.8%) of the 1,608 SAEs experienced by drug-treated participants according to trial summaries (n=142) were also reported in associated journal articles. This proportion varied widely between the drugs, from 14.8% of SAEs in atomoxetine trials to 114.6% in aripiprazole trials (see Table 2). The number of SAEs per patient for most drugs were

lower in articles (0.03, range: 0.003 - 0.07) than in associated summaries (0.05, range: 0.02 – 0.13). Trial summaries with no associated article averaged the highest number of SAEs per patient (0.07, range: 0.01 – 0.14).

Half or more of the 142 trial summary-journal article pairs were discordant in reporting the number (49.3%) or description (67.6%) of SAEs (Table 4). In half of these pairs, the reported number of SAEs differed by more than 20% between the two sources.

Both journal articles and associated trial summaries failed to describe a substantial proportion of SAEs. Most cases of death (62.3%) and suicide (53.3%) cited in trial summaries were not reported in associated journal articles (Table 3).

The 34 trial summaries with zero SAEs were 2.35 (95% confidence interval, 1.58 to 3.49; P<0.001) times as likely to have an associated journal article reporting this data consistently with the trial summary data as were the 181 summaries with 1 or more SAEs.

Explanations for Discrepant Reporting

Seventy (49.3%) of the 142 trial summary-journal article pairs were discrepant in SAE reporting. Nearly half of these instances might be explained by differences between sources in the study length or phase being reported (25%) or in the reporting criteria used (24.3%). Table 5 provides examples of each of these forms of discrepant reporting. Importantly, while some journal articles appeared to apply more restrictive reporting criteria that might lead to omitting certain data, the many articles that did report exact SAE numbers often did so regardless of presumed causality to the study drug. For example, articles and summaries for olanzapine trials 3131 and 7031 reported all SAEs even though some events were thought to be unrelated to the study drug. Yet, the article for olanzapine trial 4414 separately details SAEs thought to be related

and unrelated to the drug [20]. Thus, no clear or consistent pattern on SAE reporting criteria emerged from this sample of journal articles.

Another one-third (32.9%) of discrepancies appear to be simple failures of journal articles to report complete SAE data (see Table 5). In a minority (13%) of cases, however, the journal article provided more precise data or a higher number of SAEs than the trial summary. The article for aripiprazole trial CN138-050, for example, cites 6 SAEs in drug-treated participants [21], while the summary states only that the incidence of SAEs was low.

Post Hoc Analysis of Clinical Trial Summary Availability

In December 2011, clinicalstudyresults.org was removed from the Internet for unknown reasons. The Internet archive for the website (found here: Internet archive) suggests that the expansion of other registries made clinicalstudyresults.org seem redundant from industry's perspective [22]. One year after this removal of the registry, we cross-checked our data source by searching for each of the 244 trial summaries on clinicaltrials.gov. (In that database, the U.S. Food and Drug Administration Amendment Act [FDAAA] of 2007 newly mandated trial sponsors to include summary reporting of results for trials that were initiated after or ongoing as of late 2007.) Our search revealed that 139 (57%, range across drugs: 25% - 80%) of the 244 trials were registered on clinicaltrials.gov, but only 15 of these (10.8%, range across drugs: 0% - 39%) had posted study results. In October 2013, nearly two years after the clinicalstudyresults.org takedown, these numbers had only slightly budged, with 19 registered trials now reporting study results. While nearly all (99%) of the trial summaries not currently registered on clinicaltrials.gov have trial start or completion dates prior to 2007, 75% of trial summaries that *are* registered on the website also have pre-2007 trial dates. In the interest of openness and transparency, we created a publicly accessible website (www.rxarchives.com)

where all 244 trial summaries are posted in pdf format and freely available for download. *[Note to reviewers: the website, rxarchives.com, will become live at the time of this manuscript's publication]*

DISCUSSION

This study demonstrates that a substantially lower number of SAEs appear in published journal articles than registered trial summaries of antidepressant and antipsychotic drug trials, and shows further that both sources for drug information are often inconsistent or ambiguous in SAE reporting. In this study, 43.2% of all SAEs appearing in 142 trial summaries posted on an online registry across six psychotropic drugs were not reported in the first associated stand-alone journal articles listed by the drug's manufacturer. Failure to describe the nature of SAEs was also common in both sources. Given that many consumers of psychotropic drugs take these medications for months or years, that approximately one-quarter of journal articles reported only acute phase results of longer-term trials and that the median study length in trial summaries with an associated journal article (12 weeks) was four weeks shorter than in trials without a journal article highlight an additional attrition of evidence on longer term outcomes.

These findings are congruent with other recent analyses demonstrating more complete outcomes information in registered clinical trial summaries compared to published journal articles [9], although examination of full clinical study reports reveals that both of the latter sources suffer from incomplete reporting of key data [10]. Similar to our results, Riveros and colleagues [9] found that registered trial summaries (99%; present study 90%) more often report data on serious adverse events compared to published articles (63%; present study 60%). However, in an analysis comparing publicly available data in registered clinical trial summaries and journal publications to full clinical study reports submitted to a regulatory agency for drug

products, the former sources reported complete information on harms outcomes significantly less (~25%) than clinical study reports (87% of harms outcomes reported completely) [10]. SAEs, specifically, were reported completely only 51% of the time in journal articles and trial summaries, and 30% of SAE outcomes were not reported at all in these sources. In their analysis of full clinical study reports on the influenza drug Tamiflu, Doshi, Jefferson, and Del Mar [3] are alarmed by the important data remaining unknown to most physicians when clinical trial information is limited to the published journal literature. The occurrence of SAEs and the rationales for classifying events as adverse are among many possible discoveries in clinical study reports that can markedly alter a drug's benefit-to-risk profile. While publication bias of this sort in the literature has long been acknowledged or suspected [23-25], the present study clarifies the degree to which such bias distorts the perception of important harms outcomes (i.e., number and nature of SAEs) across two classes of popularly used psychotropic drugs. Also, this study adds to the evidence base questioning whether information posted in online clinical trial registries represents meaningful improvement.

For another 102 trials with no associated stand-alone journal article in the present study, the clinical trial summaries report an additional 1,423 SAEs and represent the only publicly available data source on these trials. In a recent examination of 585 large randomized trials registered on clinicaltrials.gov, 29% had no associated journal publication and most (78%) of those also had no results available on the clinicaltrials.gov registry [26]. Riveros and colleagues [9] found that 50% of 594 randomly sampled controlled drug trials on clinicaltrials.gov had no corresponding published article. These findings highlight the necessity for clinicians, researchers, and decision-makers to consult multiple sources in order to achieve a comprehensive and more complete appraisal of drugs' safety profile, although again, clinical trial summaries are

themselves limited by incomplete reporting [10, 27] and by regulatory policies that require registration of only recent [1] or new trials [28].

Our post hoc analysis further revealed that, while 57% (139/244) of the present sample of trial summaries are registered on clinicaltrials.gov, only 7.8% (19/244) are available on the registry with results. Three-quarters of these currently registered trials have trial start or completion dates prior to 2007, thereby suggesting that actual registration practices on clinicaltrials.gov may be more inclusive than the minimum requirements set out by the FDAAA. Access to the full evidence base of drugs currently in use, including recent studies and those conducted prior to widespread deployment of registries, is essential for sound treatment decision-making and the assurance of present day patient safety [10, 29], but the important efficacy and harms information contained in these 225 trials on six psychotropic drugs has been lost or scattered. As of this writing, Pfizer (sertraline and ziprasidone) and Bristol-Myers Squibb (aripiprazole) company websites include trial summaries or links to clinicaltrials.gov only for trials completed or ongoing as of 2007, in accordance with FDAAA guidelines. All clinical trial summaries included in the present analysis for atomoxetine, duloxetine, and olanzapine are available on Eli Lilly's company website. Some data, then, have been lost to the evidence base with the removal of clinicalstudyresults.org, while other data are still available but no longer accessible through a single repository. The important harms data contained in the present body of trial summaries provides further support for the recommendation that all ongoing, recent, and archive drug trials for all new and existing drugs be made available to clinicians and consumers in a clear and accessible format, including links between all trial-related documents (journal articles, registry records, trial protocol, and so on) for transparent navigation of each trial component to the core study [10, 30, 31].

The present study has important limitations and strengths. First, although participating industry trial sponsors had posted on their respective websites statements of their commitment to posting all trial results in a timely manner on clinicalstudyresults.org, the completeness and accuracy of trial summaries on clinicalstudyresults.org could not be verified. However, since our crosscheck of summaries on clinicaltrials.gov revealed that few of these trials were transferred with results, our present analysis provides a glimpse on unique trial evidence that a contemporary standard database fails to capture. Second, only the first stand-alone journal article for each trial was included in this analysis. For trials with multiple publications, additional information on SAEs might appear in subsequent articles. However, this possibility might be slight as the median number of journal articles per trial summary was one, and over half of total articles listed for the six drugs were pooled or sub-set analyses or conference abstracts. We do not know whether the trends observed in the 142 trial summary-journal article pairs would hold for the other 102 trials. Finally, the results of this study cannot be generalized to other drugs and drug classes, but do add to the substantial body of empirical findings demonstrating poor adverse event assessment and reporting practices and a distortion of evidence through selective reporting of industry-sponsored psychotropic drug research [24, 32-35].

The integrity of the medical treatment knowledge base preserves sound clinical practice and ensures patient safety. If nearly half of serious adverse events in psychotropic drug research are not reported in journal articles and many more can be found in sources not easily accessed by relevant treatment decision-makers [3, 10, 36], then, without integrating multiple data sources, benefit-to-harm assessments made by groups constructing clinical guidelines and by individual clinicians making prescription decisions are based on incomplete evidence and likely biased toward underestimating risks. Multiple solutions to the grave problem of incomplete reporting of

clinical trials have been proposed, and some recent strides have been made. Some suggest shifting toward public funding and control of drug research in order to produce credible information accessible and transparent to all stakeholders [37-40]. Some propose to treat failures to disclose complete knowledge of adverse effects from clinical trials as criminal offenses requiring criminal prosecution of responsible individuals and companies [41]. At the same time, ongoing campaigns have gained momentum across the United Kingdom in calling for pharmaceutical manufacturers to share clinical study reports on all drugs in use [31] and in the United States for sharing clinical trial datasets with independent scientists [42]. Many agree, however, that regulatory requirements for registering new and ongoing studies does not adequately protect the millions of patients currently taking prescription drugs [10, 31], and the pharmaceutical industry has been slow and resistant to accepting the level of openness that scientists and the public have been calling for [31, 43].

The present findings highlight inconsistencies in harms-related reporting between published articles and trial registry summaries of psychotropic drugs, and indicate that clinical decisions regarding drug use may be based on substantially truncated evidence. Policy discussions in this area should consider to what extent patients who use drugs, clinicians who prescribe drugs and the public who finance most of their use deserve access to complete and accurate scientific data from drug trials.

Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; 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.

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Contributors: SH and DC conceived the idea of the study and were responsible for the design of the study. SH and RJ were responsible for the acquisition of the data, for undertaking data coding and analysis, and produced the tables. DC also contributed to data coding, and provided critical input into the analysis and interpretation of results. The initial draft of the manuscript was prepared by SH and then circulated repeatedly among all authors for critical revision.

Data Sharing: All clinical trial summaries that were analysed in this study have been uploaded by the first author (S.H.) to a publicly-accessible website (www.rxarchives.com) for download.

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Figure 1. Clinical trial summary search results

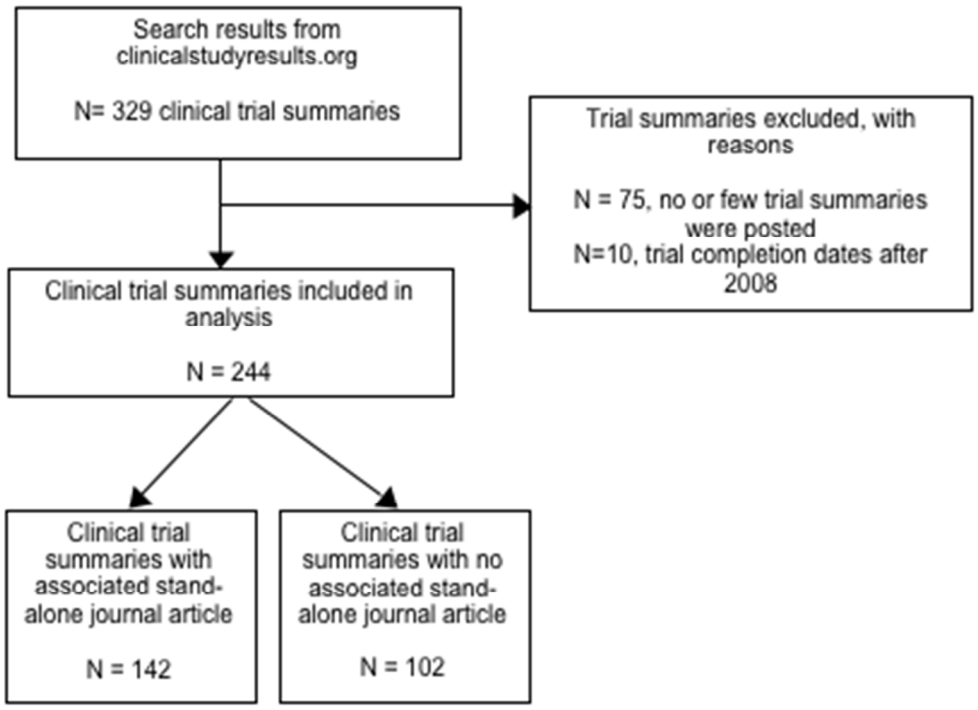

Table 1. Description of included studies

	N	Modal trial completion or article publication year	Average (median) number of publications per trial[a]	Average years from trial completion to article publication	Average (median) trial length in weeks	Maximum trial length in weeks	Number of drug treated participants (% as reported in summaries)	Total no. participants
Aripiprazole								
Trial summary	28	2006	0.62 (1)	2.6	20.8 (8)	140	5,809	9,935
Journal article	28	2009	--	--	10.7 (8)	52	5,696 (98)	9,728
Unpublished trial summary[b]	21	2003	--	--	29.9 (26)	94	6,896	8,112
Olanzapine								
Trial summary	33	2000	1.78 (1)	2.7	26.5 (24)	78	8,515	12,136
Journal article	33	2002	--	--	16.8 (6)	78	8,225 (97)	11,932
Unpublished trial summary	18	2005	--	--	18.7 (19)	48	3,120	4,997
Ziprasidone								
Trial summary	8	2005	0.79 (0)	3.8	17.1 (12)	60	910	1,399
Journal article	8	2007	--	--	10.5 (10)	27	910 (100)	1,399
Unpublished trial summary	21	2008	--	--	38.4 (12)	320	3,268	4,459
Atomoxetine								
Trial summary	31	2005	1.76 (1)	2.2	35.9 (18)	181	4,313	7,094
Journal article	31	2007	--	--	16.7 (10)	97	4,138 (96)	6,975
Unpublished trial summary	20	2006	--	--	35.7 (24)	104	3,640	4,469
Duloxetine								
Trial summary	35	2005	4.69 (3)	2	27.1 (13)	103	14,185	18,334
Journal article	35	2007	--	--	22.8 (13)	103	14,185 (100)	18,334
Unpublished trial summary	13	2004	--	--	24.2 (15)	62	2,115	3,413
Sertraline								
Trial summary	7	2003	1.53 (1)	2.9	37.7 (22)	128	2,147	2,326
Journal article	7	2005	--	--	22.9 (22)	52	2,147 (100)	2,326
Unpublished trial summary	9	2001	--	--	15.4 (10)	36	1,045	1,541
All Drugs								
Trial summary	142	2005	2 (1)	2.5	27.8 (12)	181	35,879	51,224
Journal article	142	2007	--	--	16.7 (11)	103	35,269 (98)	50,694
Unpublished trial summary	102	2006	--	--	28.8 (16)	320	20,084	26,992

[a]Average and median number of publications reflect all publications listed on the trial summary cover page, including stand-alone journal articles, meta-analyses, sub-set analyses, and conference abstracts.
[b]Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

Table 2. Number of serious adverse events (SAEs) reported in trial summaries and journal articles for drug-treated participants

	Number (%) of studies that report the number of SAEs[a]	Number of SAEs (% as reported in associated trial summaries)	Number of SAEs per patient treated[b]
Aripiprazole			
Trial summary (n=28)	26 (92.9)	364	0.06
Journal article (n=28)	27 (96.4)	417 (114.6%)	0.07
Unpublished trial summary[c] (n=21)	20 (95.2)	504	0.07
Olanzapine			
Trial summary (n=33)	28 (84.8)	544	0.06
Journal article (n=33)	11 (33.3)	66 (12.1%)	0.008
Unpublished trial summary (n=18)	17 (94.4)	302	0.10
Ziprasidone			
Trial summary (n=8)	7 (87.5)	117	0.13
Journal article (n=8)	5 (62.5)	53 (45.3%)	0.06
Unpublished trial summary (n=21)	21 (100.0)	446	0.14
Atomoxetine			
Trial summary (n=31)	25 (80.6)	88	0.02
Journal article (n=31)	14 (45.2)	13 (14.8%)	0.003
Unpublished trial summary (n=20)	17 (85.0)	35	0.01
Duloxetine			
Trial summary (n=35)	32 (91.4)	453	0.03
Journal article (n=35)	27 (77.1)	349 (77%)	0.02
Unpublished trial summary (n=13)	12 (92.3)	117	0.06
Sertraline			
Trial summary (n=7)	7 (100.0)	42	0.02
Journal article (n=7)	2 (28.6)	16 (38.1%)	0.007
Unpublished trial summary (n=9)	8 (88.9)	19	0.02
All Drugs			
Trial summary (n=142)	125 (88.0)	1,608	0.05
Journal article (n=142)	85 (59.9)	914 (56.8%)	0.03
Unpublished trial summary (n=102)	95 (93.1)	1,423	0.07

[a]The figures in this column indicate those publications that reported the number of SAEs that occurred. Some publications contained no statement about the occurrence of SAEs or contained an ambiguous statement without specifying the actual number of SAEs, such as "No SAEs thought to be related to study medication occurred."
[b]The numerator equals the number of events; the denominator equals the total number of drug-treated participants, as reported in Table 1.
[c]Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

Table 3. Number of deaths, suicide- and homicide-related events, and psychiatric serious adverse events in drug-treated participants

	Death	Suicide, completed	Suicidal ideation, attempts, injury	Homicidal ideation	New or worsened psychiatric symptoms	Total
Aripiprazole						
Trial summary (n=28)	79	1	4	0	79	163
Journal article (n=28)	27 (34.2)[a]	1 (100.0)	5 (125.0)	0	66 (83.5)	99 (60.7)
Unpublished trial summary[b] (n=21)	15	1	10	0	92	118
Olanzapine						
Trial summary (n=33)	50	9	18	0	85	162
Journal article (n=33)	19 (38.0)	1 (11.1)	4 (22.2)	0	14 (16.5)	38 (23.5)
Unpublished trial summary (n=18)	7	3	21	1	95	127
Ziprasidone						
Trial summary (n=8)	0	1	13	1	30	45
Journal article (n=8)	0 (0)	1 (100.0)	5 (38.5)	1 (100.0)	14 (46.7)	20 (44.4)
Unpublished trial summary (n=21)	18	1	23	3	141	186
Atomoxetine						
Trial summary (n=31)	0	0	7	0	6	13
Journal article (n=31)	0	0	0 (0)	0	0 (0)	0 (0)
Unpublished trial summary (n=20)	1	0	5	0	5	11
Duloxetine						
Trial summary (n=35)	11	4	40	0	27	82
Journal article (n=35)	11 (100.0)	4 (100.0)	33 (82.5)	0	21 (77.8)	69 (84.1)
Unpublished trial summary (n=13)	3	0	10	0	20	33
Sertraline						
Trial summary (n=7)	11	0	5	0	11	27
Journal article (n=7)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)
Unpublished trial summary (n=9)	1	0	10	1	4	16
All Drugs						
Trial summary (n=142)	151	15	87	1	238	492
Journal article (n=142)	57 (37.7)	7 (46.7)	47 (54.0)	1 (100.0)	115 (48.3)	227 (46.1)
Unpublished trial summary (n=102)	45	5	79	5	357	491

[a]Percent as reported in associated trial summaries.
[b]Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

Table 4. Percentage of trial summary -journal article pairs that report serious adverse event (SAE) data consistently across sources

Summary-Article Pairs	Number of SAEs		Description of SAEs
	Consistent across sources	> 20% difference across sources	Consistent across sources
Aripiprazole (n=28)	67.9	25.0	28.6
Olanzapine (n=33)	27.3	72.7	30.3
Ziprasidone (n=8)	37.5	37.5	37.5
Atomoxetine (n=31)	54.8	45.2	42.0
Duloxetine (n=35)	62.9	37.1	31.4
Sertraline (n=7)	28.6	71.4	14.3
All Drugs (n=142)	50.7	49.2	32.4

Table 5. Explanations for Discrepant Reporting of SAEs between Journal Articles and Trial Summaries

Category of discrepant reporting	Specific explanation for discrepant reporting	Example
Difference in study length or phase reported	Reporting only one phase of a multi-phase trial	In atomoxetine trial 6962, the journal article cites zero SAEs in the 10-week acute phase [44]; three SAEs that were thought to be related to study medication (suicidal ideation, aggression, and self-injurious behavior) occurred in the 22-week extension phase reported in the trial summary.
	Not reporting SAEs that occurred during follow-up	In olanzapine trial 3045, the journal article stated "there were no deaths during the study," but failed to cite the death that occurred within 30 days after the study [45].
Difference in reporting criteria used	Not reporting SAEs that were presumed to be unrelated to the study drug	In these cases, journal articles would either make no mention at all of SAEs or would include a statement implying that SAEs did occur but without providing an exact figure, such as "No patients in either treatment group had a serious adverse event that was considered study medication related" [46]. In atomoxetine trial 5831, two SAEs thought to be "unlikely but possibly related" to the study drug were unreported in the associated journal article [47].
	Not reporting SAEs that were not statistically significantly different between treatment groups	In olanzapine trial 1032, 28 SAEs occurred in the randomized phase on which the journal article presents results. The journal article, however, contains no statement about SAE occurrence presumably because, as the trial summary indicates, there were no statistically significant differences in SAEs between treatment groups [48].
Apparent selective reporting of data	Omissions of SAE data	In sertraline trial 1060, the trial summary cites 5 SAEs in drug-treated participants, one of which occurred in the open-label phase and was thought by investigators to be related to the study drug. The journal article reports on the full length of the trial (open and double-blind phases), but only includes this statement related to SAEs: "No subjects had serious adverse events related to study treatment in either treatment group *during the double-blind phase*" [49] [emphasis added]. In olanzapine trial 2354, the journal article reports a lower number of SAEs than cited for the same study phase in the trial summary, and describes "the majority" of SAEs as "worsening of the illness" [50]. The trial summary reports a higher incidence of SAEs and more precisely details the events as suicidal ideation, suicide attempt, mania, and so on.

Appendix Table 1. Trial completion dates and time to journal article publication for six psychotropic drugs on clinicalstudyresults.org

	1999 or earlier	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009 or later
Aripiprazole											
Number of completed trials	0	0	3	5	10	5	4	11	8	3	3
(% published as stand-alone article)[a]			(66.7)	(40)	(40)	(100)	(75)	(54.5)	(37.5)	(100)	(0)
Average years to article publication	--	--	3	5	5	2.4	3	2	1.7	1	n/a
Olanzapine											
Number of completed trials	12	7	2	7	3	0	7	8	4	1	0
(% published as stand-alone article)	(91.7)	(100)	(100)	(85.7)	(33.3)		(28.6)	(37.5)	(0)	(100)	
Average years to article publication	2.2	2.3	4	3.5	3	--	3	3	n/a	1	--
Ziprasidone											
Number of completed trials	0	0	0	2	5	4	7	2	1	8	5
(% published as stand-alone article)				(50)	(20)	(25)	(42.9)	(100)	(0)	(0)	(0)
Average years to article publication	--	--	--	5	2	6	3.7	3	n/a	n/a	n/a
Atomoxetine											
Number of completed trials	1	2	6	6	6	7	8	12	3	0	0
(% published as stand-alone article)	(100)	(100)	(66.7)	(83.3)	(66.7)	(71.4)	(75)	(16.7)	(66.7)		
Average years to article publication	3	2	2.3	2.6	2.8	2.8	1.8	1	1	--	--
Duloxetine											
Number of completed trials	3	1	6	4	5	7	10	4	8	0	1
(% published as stand-alone article)	(0)	(100)	(66.7)	(100)	(100)	(57.1)	(90)	(75)	(62.5)		(0)
Average years to article publication	n/a	2	1.8	3	2.8	2	2.1	1.3	1.4	--	n/a
Sertraline											
Number of completed trials	4	0	3	0	5	0	2	0	2	0	0
(% published as stand-alone article)	(75)		(0)		(80)		(0)		(0)		
Average years to article publication	4.3	--	n/a/	--	1.8	--	n/a	--	n/a	--	--
All Drugs											
Number of completed trials	20	10	20	24	34	23	38	37	26	12	10
(% published as stand-alone article)	(75)	(100)	(60)	(75)	(56)	(65)	(60)	(43)	(38)	(33)	(0)
Average years to article publication	3.2	2.1	2.8	3.8	2.9	3.3	2.7	2.1	1.4	1	n/a

[a] Meta-analyses and sub-set analyses published in journals and conference abstracts are not included in the percent published.

Appendix Table 2: Drug-treated participants and serious adverse events (SAEs) among ten trial summaries of clinical trials completed in 2009 or later (excluded from the published analysis)

	Number of excluded trial summaries	Number of drug- treated participants	Total number of SAEs in drug-treated participants	Number of SAEs			
				Death	Suicide, completed	Suicidal ideation, attempt, injury	New or worsened psychiatric symptoms
Aripiprazole	3	676	39	1	1	1	2
Olanzapine	0	NA	NA	NA	NA	NA	NA
Ziprasidone	5	1436	124	3	2	9	57
Atomoxetine	0	NA	NA	NA	NA	NA	NA
Duloxetine	1	657	2	0	0	0	1
Sertraline	1	157	2	0	0	1	0
All Drugs	10	2926	167	4	3	11	60

STROBE Statement

"Differences in Reporting Serious Adverse Events in Industry-Sponsored Clinical Trial Registries and Journal Articles on Antidepressant and Antipsychotic Drugs – A Cross-sectional Study"

	Page No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4	Explain the scientific background and rationale for the investigation being reported
Objectives	4-5	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6-8	Present key elements of study design early in the paper
Setting	6-7	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6-7	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
Variables	8-9	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	6-9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	8	Describe any efforts to address potential sources of bias
Study size	6-7	Explain how the study size was arrived at
Quantitative variables	9	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	9	(*a*) Describe all statistical methods, including those used to control for confounding
	n/a	(*b*) Describe any methods used to examine subgroups and interactions
	n/a	(*c*) Explain how missing data were addressed
	n/a	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	n/a	(*e*) Describe any sensitivity analyses

Results		
Participants	6-7	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	6-7	(b) Give reasons for non-participation at each stage
	n/a	(c) Consider use of a flow diagram
Descriptive data	10	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	n/a	(b) Indicate number of participants with missing data for each variable of interest
Outcome data	10-12	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	10-12	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval).
	n/a	(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	13	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	14-16	Summarise key results with reference to study objectives
Limitations	17	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	14-16, 18	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	17	Discuss the generalisability (external validity) of the study results
Other information		
Funding	19	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Summary ID#4091

Clinical Study Summary: Study F1J-MC-HMAT Study Group B

Title of Study: Duloxetine Versus Placebo and Paroxetine in the Acute Treatment of Major Depression	
Investigator(s): This multicenter study included 20 principal investigators.	
Study Center(s): There were 22 study sites (two investigators had satellite sites) in the United States.	
Length of Study: 11 months Date first patient enrolled: 09 March 2000 Date last patient completed: 06 February 2001	**Phase of Development:** 3

Objectives: The primary objective of this study was to demonstrate that duloxetine 40 mg twice daily (BID) is superior to placebo in the acute treatment of patients with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)–defined major depressive disorder (MDD).

The secondary objectives of this study were:

- To compare the safety of duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine using information on discontinuation rates, treatment-emergent adverse events (TEAEs), discontinuation-emergent adverse events, laboratory analyses, vital signs, and electrocardiograms (ECGs).
- To compare the efficacy of duloxetine 40 mg BID with paroxetine as measured by a noninferiority test of mean 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) total scores at Visit 8. Data from each of the two studies (HMAT Study Group A and Study Group B) will be combined for this comparison.
- To assess the efficacy of duloxetine 20 mg BID and duloxetine 40 mg BID compared with placebo as measured by response and remission rates.
- To compare the time to onset of action (defined as time to meeting responder criteria) of duloxetine 20 mg BID, duloxetine 40 mg BID, and paroxetine.
- To compare the efficacy of duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine on anxiety symptoms associated with depression as measured by mean endpoint scores on the Hamilton Anxiety Rating Scale (HAMA) and the anxiety subscale of the $HAMD_{17}$.
- To compare the efficacy of duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine as measured by mean endpoint scores (after adjusting for baseline differences) on the Clinical Global Impressions of Severity scale (CGI-Severity), the Montgomery and Asberg Depression Rating Scale (MADRS), $HAMD_{17}$ subfactor scores, and endpoint scores on the Patient's Global Impressions of Improvement scale (PGI-Improvement).
- To compare the efficacy of duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine on somatic complaints of pain using the Somatic Symptom Inventory scale (SSI) and Visual Analog Scales (VAS).
- To compare the impact of treatment with duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine on sexual functioning as measured by the Arizona Sexual Experiences Scale (ASEX).
- To compare the impact of treatment with duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine on quality of life as measured by the Quality of Life in Depression Scale (QLDS), and on medical resource utilization and work productivity as measured by the Resource Utilization scale.

Study Design: Multicenter, parallel, double-blind, randomized, placebo- and active comparator-controlled study with blinded placebo lead-in and placebo lead-out. The protocol consisted of two identical studies conducted in parallel and reported separately (Study Group A and Study Group B). The study consisted of two study periods. Study Period I was the 1-week screening phase of the study, and Study Period II was an 11-week acute therapy phase in which patients were assessed weekly from Visit 2 (Week 0) to Visit 5 (Week 3) and every other week from Visit 5 (Week 3) to Visit 9 (Week 11). This study design employed double-blind, variable-duration placebo lead-in and lead-out periods to blind patients and investigators at the start and end of active therapy. Figure HMATb.1 illustrates the study design.
Number of Patients: Planned: 356 patients (89 per treatment group) Randomized: 86 Duloxetine 20 mg BID; 91 Duloxetine 40 mg BID ; 89 Placebo; 87 Paroxetine 20 mg QD. Completed: 55 Duloxetine 20 mg BID; 53 Duloxetine 40 mg BID; 52 Placebo; 49 Paroxetine 20 mg QD.
Diagnosis and Main Criteria for Inclusion: Male and female outpatients of at least 18 years of age with a primary diagnosis of MDD as defined by the DSM-IV, and confirmed by use of the Mini International Neuropsychiatric Interview (MINI). Patients were required to have a $HAMD_{17}$ total score ≥15 and a CGI-Severity total score ≥4 at both Visit 1 and Visit 2.
Test Product, Dose, and Mode of Administration: Duloxetine capsules, 20 mg; patients took 40 mg orally twice daily or 20 mg orally twice daily.
Duration of Treatment: Duloxetine: 8 weeks Paroxetine: 8 weeks Placebo: 11 weeks
Reference Therapy, Dose, and Mode of Administration: Paroxetine 20 mg capsules; patients took 20 mg orally once daily. Placebo capsules
Variables: Efficacy: The primary efficacy measure was the $HAMD_{17}$ total score. Secondary efficacy measures included $HAMD_{17}$ response rates (50% reduction from baseline to endpoint), $HAMD_{17}$ remission rates (endpoint score ≤7), time to sustained response, and time to sustained remission. Other secondary measures included the $HAMD_{17}$ subfactors and individual items, MADRS, CGI-Severity, PGI-Improvement, HAMA, Somatic Symptom Inventory (SSI) 26- and 28-item scale, and Visual Analog Scales (VAS) for pain. Safety: Safety was evaluated through the collection and reporting of discontinuation rates, TEAEs, discontinuation-emergent adverse events, laboratory analyses, vital signs, ECGs, and the ASEX. Health Outcomes: Health outcomes were evaluated using the QLDS scale and Health Resource Utilization scales. Health Resource Utilization results will not be reported in this synopsis.

Evaluation Methods:

Statistical:

The primary efficacy comparison was between duloxetine 40 mg BID and placebo, based on the likelihood-based repeated measures analysis. The terms in the repeated measure analysis model included treatment, visit, investigative site, baseline score, and the interactions of visit with treatment and baseline score. For secondary measures, an analysis of covariance (ANCOVA)/analysis of variance (ANOVA) model containing terms for treatment, investigator, and baseline score (no baseline score term in ANOVA model) was used for continuous variables. Categorical variables such as response and remission rates were evaluated using Fisher's exact test and the Cochran-Mantel-Haenszel (CMH) chi-square test with investigative site as strata. Time to event data, such as time to onset of action, were analyzed using the Kaplan-Meier method, and the treatment group differences were tested by the log-rank and Wilcoxon tests.

An intent-to-treat (ITT) principle was applied in all efficacy and safety analyses. For all total scores calculated from individual items, if any of the individual items was missing, the corresponding total score was considered missing. Sites with fewer than 8 randomly assigned patients with baseline and at least one postbaseline (Visit 4 to Visit 8) $HAMD_{17}$ total score were pooled. If this resulted in a pooled site with fewer than 8 patients, these patients were pooled with the next smallest site. For efficacy and safety analyses, treatment group differences were tested at a 2-sided significance level of 0.05.

The planned sample size (356 patients) provides 83% power to detect a difference between the duloxetine 40 mg BID and placebo groups of 3.25 points in mean change from baseline to endpoint of the $HAMD_{17}$ total score, assuming a common standard deviation of 7.0, 90% of patients would provide at least one baseline and one postbaseline assessment, and using a two-sided test with α=0.05. Using data pooled from Study Group A and Study Group B, this sample size also provides 80% power to test the non-inferiority of duloxetine 40 mg BID compared with paroxetine using a one-sided 97.5% confidence interval and an equivalence limit of –2.2 for mean $HAMD_{17}$ scores.

Summary:

Disposition/Demographics (Table HMATb.1): A total of 353 patients were randomly assigned and enrolled into the study. Of these, 209 patients completed the acute therapy phase (placebo, n=52; duloxetine 20 mg BID, n=55; duloxetine 40 mg BID, n=53; paroxetine 20 mg QD, n=49) and 206 completed the entire study. The percentages of patients who discontinued for any reason during the acute therapy phase were similar among the four treatment groups. No statistically significant differences were observed among treatment groups with regard to age, gender, origin, or height. Patients had a mean age of approximately 40 years, with the majority being Caucasian and female.

Efficacy Measures (Tables HMATb.2, Table HMATb.3)**:** Patients treated with duloxetine at both doses (20 mg BID and 40 mg BID) had statistically significantly greater improvement in the primary efficacy measure ($HAMD_{17}$ total score) compared with placebo-treated patients, by repeated measures analysis. Paroxetine-treated patients did not differ statistically significantly from the placebo group on this measure. Mean change analyses revealed the same results. Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement in scores on the primary efficacy measure ($HAMD_{17}$ total score) compared with paroxetine-treated patients at endpoint.

Patients treated with duloxetine 40 mg BID met the criteria for treatment response and remission at endpoint statistically significantly more frequently than did patients treated with placebo. Patients treated with either duloxetine 40 mg BID or paroxetine had statistically significantly shorter time to first response than did patients treated with placebo.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the $HAMD_{17}$ subfactor scores of Anxiety/Somatization, Core Factor, Maier, and Retardation as compared with placebo-treated patients.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the MADRS total score compared with placebo-treated patients, by repeated measures analysis. Mean change analysis revealed the same result. Duloxetine 20 mg BID, paroxetine- and placebo-treated patients did not differ statistically significantly on this measure.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the HAMA scale compared with placebo-treated patients (despite the fact that this trial excluded patients with primary anxiety disorders). Mean change analyses revealed the same result. Paroxetine- and placebo-treated patients did not differ statistically significantly on this measure.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the Visual Analog Scale (VAS) for overall pain severity compared with placebo-treated patients, and showed marginally statistically significantly greater improvement on the VAS for amount of time in pain while awake. Mean change analyses revealed the same results.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the Quality of Life in Depression Scale (QLDS), and showed a statistically significantly greater percentage of patients with reductions in the types of health care providers visited and the number of visits to health care providers, compared with placebo-treated patients.

There were statistically significantly fewer discontinuations due to perceived lack of efficacy for patients treated with both doses of duloxetine compared with placebo-treated patients.

Using 2.2 as the noninferiority margin, it is shown that duloxetine 40 mg BID treatment was noninferior to paroxetine treatment using either repeated measure analysis or mean change analysis. In addition, even when using a more stringent noninferiority margin than 2.2 (namely, using one-half of the absolute gain of paroxetine over placebo), it remains true that duloxetine 40 mg BID treatment was noninferior to paroxetine treatment using repeated measures analysis.

Safety — Acute Therapy Phase:

Deaths/Serious Adverse Events/Discontinuations Due to Adverse Events: No patients died during this study. Two patients experienced serious adverse events postrandomization. One patient receiving duloxetine 40 mg BID had an accidental injury falling from a horse, suffering a concussion and a subsequent seizure. One patient receiving paroxetine relapsed into alcohol abuse, suffered alcohol withdrawal symptoms, and was admitted for detoxification. In the acute therapy phase 40 (11.3%) of 353 discontinued due to an adverse event. There were no statistically significant differences among treatment groups with respect to adverse events reported as a reason for discontinuation in the acute therapy phase. The percentages of patients who discontinued for any reason were similar among the four treatment groups.

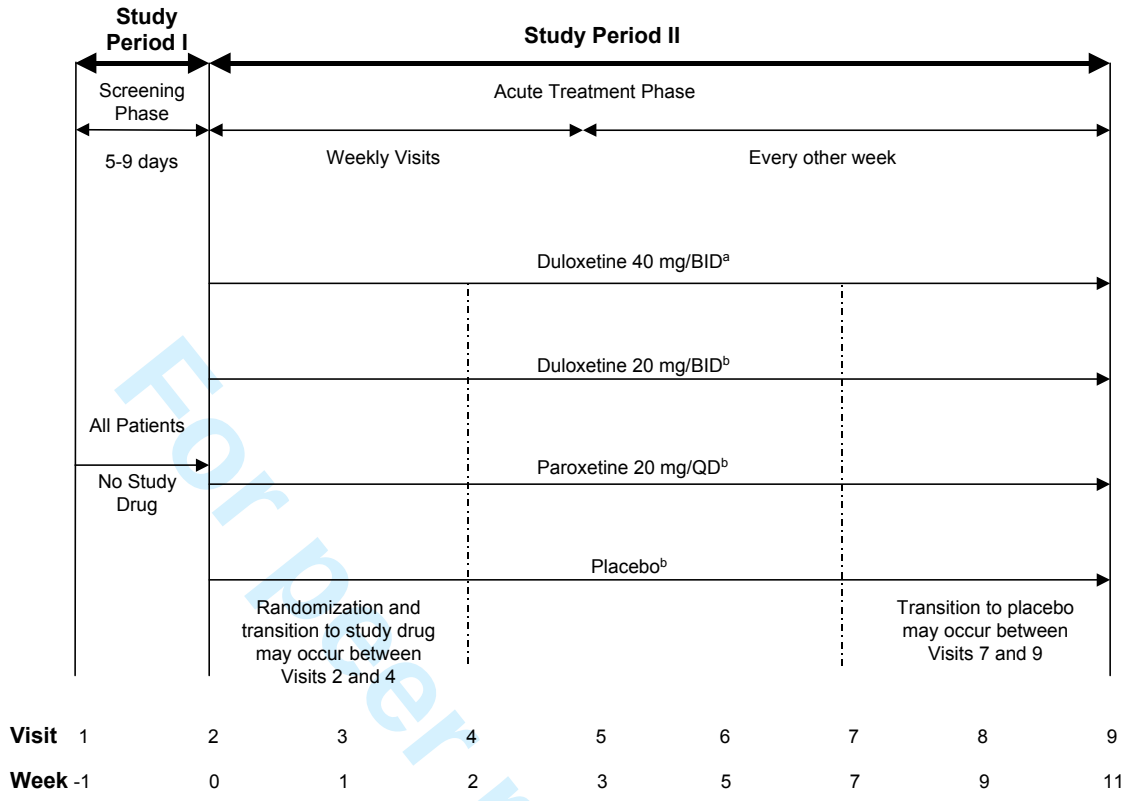

Figure HMAT.1. Illustration of study design for Protocol F1J-MC-HMAT.

Table HMATb.1. Patient Characteristics at Baseline
All Randomized Patients

Variable	PLACEBO (N=89)	DLX20BID (N=86)	DLX40BID (N=91)	PRX20QD (N=87)	Total (N=353)	p-Value
AGE: YRS						
No. Patients	89	86	91	87	353	.949**
Mean	40.14	40.69	40.89	40.25	40.50	
Median	41.28	40.05	40.83	39.25	40.29	
Standard Dev.	12.94	10.04	11.90	11.02	11.50	
Minimum	20.07	20.56	18.20	19.18	18.20	
Maximum	78.21	70.60	68.87	64.02	78.21	
HEIGHT: CM (Visit: 1)						
No. Patients	89	85	91	87	352	.556**
Mean	170.84	170.66	169.45	169.19	170.03	
Median	170.18	167.64	167.64	170.18	167.64	
Standard Dev.	9.69	9.66	10.72	9.79	9.97	
Minimum	152.40	152.40	139.70	149.86	139.70	
Maximum	198.12	200.66	195.58	193.04	200.66	
Unspecified	0	1	0	0	1	
WEIGHT: KG (Visit: 1)						
No. Patients	88	86	90	87	351	.071**
Mean	80.22	81.61	82.19	88.75	83.18	
Median	77.86	78.09	81.95	79.00	79.00	
Standard Dev.	18.93	20.33	20.87	28.97	22.74	
Minimum	45.40	51.76	43.58	45.40	43.58	
Maximum	153.91	165.26	155.72	194.31	194.31	
Unspecified	1	0	1	0	2	

Table HMATb.1. Patient Characteristics at Baseline
All Randomized Patients (concluded)

Variable	PLACEBO (N=89)	DLX20BID (N=86)	DLX40BID (N=91)	PRX20QD (N=87)	Total (N=353)	p-Value
ORIGIN: NO. (%)						
No. Patients	89	86	91	87	353	.270*
African Descent	8 (9.0)	4 (4.7)	5 (5.5)	9 (10.3)	26 (7.4)	
Western Asian	0	0	0	2 (2.3)	2 (0.6)	
Caucasian	74 (83.1)	72 (83.7)	77 (84.6)	64 (73.6)	287 (81.3)	
East/Southeast A	1 (1.1)	0	0	0	1 (0.3)	
Hispanic	6 (6.7)	9 (10.5)	9 (9.9)	12 (13.8)	36 (10.2)	
Other	0	1 (1.2)	0	0	1 (0.3)	
GENDER: NO. (%)						
No. Patients	89	86	91	87	353	.633*
Female	57 (64.0)	48 (55.8)	56 (61.5)	56 (64.4)	217 (61.5)	
Male	32 (36.0)	38 (44.2)	35 (38.5)	31 (35.6)	136 (38.5)	

Output stored as RMP.F1JO.HMAT.FINALB(DE128006)
Data from RMP.SAS.F1JM.MCHMATSW.STUDYB
* Frequencies are analyzed using a Chi-Square test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator and treatment.
XDES0001

Table HMATb.2. Summary of Efficacy and Health Outcome Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb

Variable	Treatment Group				p-Value		
	Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
$HAMD_{17}$ Total Score	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	17.19 (5.11)	18.63 (5.85)	18.06 (4.52)	17.65 (5.13)			
Mean Change (SD)	–4.16 (6.42)	–7.17 (7.97)	–7.72 (7.67)	–6.06 (8.12)	p=.022	p=.003	p=.150
LS Mean Change (SE)	–4.99 (0.81)	–7.42 (0.80)	–8.61 (0.81)[a]	–6.22 (0.82)	p=.034	p=.002	p=.285
$HAMD_{17}$ Response Rate	n=88	n=84	n=86	n=84			
Responders n (%)	27 (31%)	37 (44%)	44 (51%)	34 (40%)	.083	.009	.204
$HAMD_{17}$ Remission Rate	n=88	n=84	n=86	n=84			
Remitters n (%)	26 (30%)	29 (35%)	43 (50%)	31 (37%)	.516	.008	.334
$HAMD_{17}$ Subscale – Core	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	7.43 (2.64)	8.05 (2.53)	7.36 (2.14)	7.65 (2.43)			
Mean Change (SD)	–2.02 (3.39)	–3.37 (3.53)	–3.40 (3.14)	–3.00 (3.87)	p=.023	p=.008	p=.110
LS Mean Change (SE)	–2.64 (0.39)	–3.66 (0.38)	–4.00 (0.39)	–3.24 (0.39)	p=.060	p=.013	p=.271
$HAMD_{17}$ Subscale – Maier	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	9.26 (3.00)	9.88 (3.01)	9.47 (2.28)	9.33 (2.64)			
Mean Change (SD)	–2.53 (3.56)	–4.04 (4.25)	–4.30 (3.90)	–3.75 (4.33)	p=.028	p=.004	p=.057
LS Mean Change (SE)	–3.06 (0.44)	–4.18 (0.43)	–4.79 (0.44)	–4.03 (0.44)	p=.068	p=.005	p=.115

Table HMATb.2. Summary of Efficacy and Health Outcome Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (continued)

Variable	Treatment Group: Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	p-Value: Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
$HAMD_{17}$ Subscale – Anxiety/Somatization	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	5.48 (2.12)	6.04 (2.52)	6.07 (1.82)	5.85 (2.41)			
Mean Change (SD)	–1.06 (2.49)	–2.17 (3.08)	–2.79 (2.72)	–2.13 (3.23)	p=.046	p=<.001	p=.040
LS Mean Change (SE)	–1.38 (0.29)	–2.11 (0.28)	–2.92 (0.28)[a]	–2.11 (0.29)	p=.066	p=<.001	p=.069
$HAMD_{17}$ Subscale – Retardation/Somatization	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	6.38 (1.97)	6.96 (2.11)	6.34 (1.75)	6.81 (1.95)			
Mean Change (SD)	–1.80 (2.84)	–2.80 (3.03)	–2.63 (2.80)	–2.45 (3.15)	p=.047	p=.053	p=.263
LS Mean Change (SE)	–2.32 (0.32)	–3.08 (0.32)	–3.22 (0.32)	–2.59 (0.33)	p=.092	p=.046	p=.546
$HAMD_{17}$ Subscale – Sleep	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	2.67 (1.87)	2.76 (1.86)	2.85 (1.82)	2.54 (1.85)			
Mean Change (SD)	–0.81 (1.91)	–1.05 (2.04)	–1.02 (2.29)	–0.69 (2.16)	p=.485	p=.769	p=.827
LS Mean Change (SE)	–0.84 (0.21)	–1.04 (0.20)	–1.14 (0.21)	–0.65 (0.21)	p=.483	p=.303	p=.503

Table HMATb.2. Summary of Efficacy and Health Outcome Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (continued)

	Treatment Group				p-Value		
Variable	Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
$HAMD_{17}$ Item #1 Score	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	2.32 (0.89)	2.52 (0.80)	2.24 (0.77)	2.37 (0.79)			
Mean Change (SD)	–0.67 (1.24)	–1.08 (1.19)	–0.95 (1.02)	–0.96 (1.31)	p=.054	p=.065	p=.122
LS Mean Change (SE)	–0.89 (0.13)	–1.15 (0.13)	–1.16 (0.13)	–1.11 (0.13)	p=.174	p=.152	p=.255
MADRS	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	22.72 (8.00)	24.44 (8.05)	22.58 (6.21)	23.07 (7.51)			
Mean Change (SD)	–5.75 (9.19)	–9.11 (11.50)	–8.99 (10.08)	–8.51 (11.91)	p=.082	p=.029	p=.105
LS Mean Change (SE)	–7.43 (1.15)	–9.37 (1.14)	–10.73 (1.16)	–9.01 (1.17)	p=.227	p=.042	p=.331
CGI-Severity	n=88	n=84	n=87	n=85			
Mean Baseline (SD)	4.11 (0.73)	4.19 (0.80)	4.10 (0.51)	4.02 (0.62)			
Mean Change (SD)	–0.88 (1.21)	–1.19 (1.38)	–1.20 (1.26)	–1.06 (1.39)	p=.135	p=.078	p=.262
LS Mean Change (SE)	–1.10 (0.15)	–1.36 (0.15)	–1.42 (0.16)	–1.25 (0.16)	p=.242	p=.153	p=.507

Table HMATb.2. Summary of Efficacy and Health Outcome Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (concluded)

	Treatment Group				p-Value		
Variable	Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
PGI-Improvement	n=88	n=84	n=86	n=85			
Mean Baseline (SD)	n/a	n/a	n/a	n/a			
Endpoint Mean (SD)	3.24 (1.41)	2.93 (1.31)	2.86 (1.47)	2.99 (1.44)	p=.162	p=.079	p=.253
Endpoint LS Mean (SE)	2.87 (0.15)	2.74 (0.15)	2.52 (0.15)	2.80 (0.15)	p=.522	p=.093	p=.743
HAMA	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	14.48 (5.33)	15.25 (5.86)	14.88 (4.87)	14.49 (5.76)			
Mean Change (SD)	–3.49 (5.32)	–5.13 (6.74)	–5.86 (7.14)	–4.60 (7.36)	p=.149	p=.019	p=.257
LS Mean Change (SE)	–4.33 (0.69)	–5.45 (0.68)	–6.57 (0.69)	–5.23 (0.69)	p=.238	p=.020	p=.349
QLDS	n=80	n=76	n=78	n=72			
Mean Baseline (SD)	15.21 (7.32)	19.92 (7.37)	17.22 (7.67)	17.60 (8.49)			
Mean Change (SD)	–4.30 (8.21)	–9.29 (8.61)	–8.55 (9.39)	–7.96 (10.26)	p=.069	p=.023	p=.084
LS Mean Change (SE)	–7.87 (1.07)	–8.90 (1.04)	–10.76 (1.05)	–9.85 (1.04)	p=.483	p=.050	p=.178

Abbreviations: CGI-Severity = Clinical Global Impressions of Severity; HAMA = Hamilton Anxiety Rating Scale; $HAMD_{17}$ = 17-Item Hamilton Depression Rating Scale; MADRS = Montgomery and Asberg Depression Rating Scale; PGI-Improvement = Patient's Global Impressions of Improvement; Dulox 20 BID = duloxetine 20 mg twice daily; Dulox 40 BID = duloxetine 40 mg twice daily; Parox 20 QD = paroxetine 20 mg once daily; QLDS = Quality of Life in Depression Scale; SD = standard deviation; SE = standard error.

Note: n = the number of patients who had a baseline score and at least one nonmissing postbaseline score for that particular variable

Note: "n/a" in Global Impressions of Improvement scales indicates that a baseline score is not collected in this type of scale

Note: Mean Change – Data from mean change analysis

Note: LS Mean Change – Data from repeated measures analysis

[a] Result was statistically significant (p≤.05) compared with paroxetine 20 mg QD

Table HMATb.3. Summary of Somatic and Pain Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb

Variable	Treatment Group				p-Value		
	Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
SSI 26-Item Average	n=88	n=82	n=86	n=85			
Mean Baseline (SD)	1.68 (0.55)	1.71 (0.51)	1.71 (0.55)	1.71 (0.47)			
Mean Change (SD)	–0.13 (0.47)	–0.13 (0.35)	–0.17 (0.46)	–0.17 (0.47)	p=.700	p=.875	p=.732
LS Mean Change (SE)	–0.18 (0.05)	–0.15 (0.05)	–0.22 (0.05)	–0.22 (0.05)	p=.620	p=.621	p=.540
SSI 28-Item Average	n=88	n=82	n=86	n=85			
Mean Baseline (SD)	1.69 (0.56)	1.72 (0.51)	1.74 (0.57)	1.72 (0.49)			
Mean Change (SD)	–0.13 (0.47)	–0.13 (0.35)	–0.19 (0.46)	–0.17 (0.47)	p=.703	p=.640	p=.740
LS Mean Change (SE)	–0.18 (0.05)	–0.15 (0.05)	–0.24 (0.05)	–0.22 (0.05)	p=.636	p=.409	p=.581
VAS-Severity of Overall Pain	n=88	n=84	n=86	n=85			
Mean Baseline (SD)	24.18 (25.99)	27.02 (25.39)	25.55 (22.83)	22.22 (22.48)			
Mean Change (SD)	–3.20 (27.17)	–6.44 (23.30)	–10.34 (22.52)	–8.06 (20.26)	p=.710	p=.048	p=.071
LS Mean Change (SE)	–4.09 (2.49)	–5.08 (2.42)	–11.44 (2.49)	–9.63 (2.51)	p=.771	p=.035	p=.113

Table HMATb.3. Summary of Somatic and Pain Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (continued)

	Treatment Group				p-Value		
Variable	Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
VAS-Severity of Headaches	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	23.68 (28.58)	20.63 (23.70)	22.42 (23.30)	16.05 (20.63)			
Mean Change (SD)	–6.17 (25.39)	–3.36 (22.70)	–7.99 (24.03)	–3.40 (23.08)	p=.677	p=.470	p=.603
LS Mean Change (SE)	–6.25 (2.30)	–5.56 (2.23)	–7.90 (2.30)	–6.83 (2.32)	p=.828	p=.607	p=.859
VAS-Severity of Back Pain	n=88	n=84	n=86	n=85			
Mean Baseline (SD)	17.23 (22.76)	22.31 (26.11)	20.19 (24.61)	15.87 (18.07)			
Mean Change (SD)	–1.19 (25.30)	–6.88 (21.83)	–8.31 (24.05)	–3.36 (20.01)	p=.414	p=.094	p=.387
LS Mean Change (SE)	–2.48 (2.41)	–5.06 (2.35)	–7.67 (2.41)	–4.19 (2.43)	p=.439	p=.124	p=.612
VAS-Severity of Shoulder Pain	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	14.64 (23.56)	12.65 (19.58)	15.98 (22.24)	13.68 (22.73)			
Mean Change (SD)	–2.40 (20.09)	–2.07 (19.53)	–7.97 (21.61)	–2.71 (22.95)	p=.899	p=.081	p=.907
LS Mean Change (SE)	–2.34 (2.26)	–2.98 (2.19)	–5.67 (2.26)	–0.82 (2.26)	p=.837	p=.292	p=.631

Table HMATb.3. Summary of Somatic and Pain Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (concluded)

	Treatment Group				p-Value		
Variable	**Placebo**	**Dulox 20 BID**	**Dulox 40 BID**	**Parox 20 QD**	**Dulox 20 vs placebo**	**Dulox 40 vs placebo**	**Parox 20 vs placebo**
VAS-Interference with Daily Activities	n=88	n=84	n=86	n=85			
Mean Baseline (SD)	17.14 (25.42)	19.52 (24.66)	17.00 (21.00)	15.62 (20.91)			
Mean Change (SD)	–3.38 (26.49)	–1.94 (26.44)	–4.90 (25.39)	–3.29 (20.77)	p=.261	p=.687	p=.915
LS Mean Change (SE)	–4.31 (2.53)	–0.57 (2.45)	–6.79 (2.52)	–4.24 (2.53)	p=.281	p=.482	p=.983
VAS-Pain While Awake	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	25.73 (28.05)	34.93 (32.52)	29.23 (27.28)	28.30 (30.51)			
Mean Change (SD)	–1.95 (30.33)	–8.18 (31.49)	–10.99 (32.23)	–8.10 (32.52)	p=.787	p=.078	p=.269
LS Mean Change (SE)	–2.43 (3.32)	–2.70 (3.23)	–11.36 (3.31)	–6.02 (3.33)	p=.952	p=.055	p=.440

Abbreviations: Dulox 20 BID = duloxetine 20 mg twice daily; Dulox 40 BID = duloxetine 40 mg twice daily; Parox 20 QD = paroxetine 20 mg once daily; SSI = Somatic Symptom Inventory; VAS = Visual Analog Scales

Note: n = the number of patients who had a baseline score and at least one nonmissing postbaseline score for that particular variable

Note: Mean Change – Data from mean change analysis

Note: LS Mean Change – Data from repeated measures analysis

Table HMATb.4. Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2 Percent
All Randomized Patients
Acute Therapy Phase

	PLACEBO N=89 n(%)	DLX20BID N=86 n(%)	DLX40BID N=91 n(%)	PRX20QD N=87 n(%)	Total N=353 n(%)	p-Values* Overall	1vs2	1vs3	1vs4	2vs3	2vs4	3vs4
PATIENTS WITH >= 1 TESS	61(68.5)	73(84.9)	76(83.5)	76(87.4)	286(81.0)	.009	.013	.023	.003	.839	.666	.528
NAUSEA	2(2.2)	19(22.1)	23(25.3)	14(16.1)	58(16.4)	<.001	<.001	<.001	.001	.724	.339	.143
HEADACHE	10(11.2)	12(14.0)	17(18.7)	10(11.5)	49(13.9)	.470	.652	.211	1.00	.423	.655	.213
INSOMNIA	5(5.6)	15(17.4)	18(19.8)	7(8.0)	45(12.7)	.008	.017	.006	.564	.705	.072	.031
RHINITIS	15(16.9)	7(8.1)	5(5.5)	7(8.0)	34(9.6)	.075	.110	.018	.110	.558	1.00	.560
SOMNOLENCE	2(2.2)	15(17.4)	10(11.0)	7(8.0)	34(9.6)	.005	<.001	.033	.098	.281	.072	.613
DIZZINESS	5(5.6)	4(4.7)	15(16.5)	9(10.3)	33(9.3)	.032	1.00	.031	.278	.014	.248	.276
DRY MOUTH	3(3.4)	9(10.5)	14(15.4)	7(8.0)	33(9.3)	.042	.077	.009	.209	.377	.611	.165
DIARRHEA	7(7.9)	7(8.1)	8(8.8)	10(11.5)	32(9.1)	.851	1.00	1.00	.454	1.00	.611	.624
CONSTIPATION	3(3.4)	7(8.1)	8(8.8)	12(13.8)	30(8.5)	.095	.207	.212	.015	1.00	.331	.346
PAIN	10(11.2)	6(7.0)	3(3.3)	6(6.9)	25(7.1)	.230	.434	.047	.433	.319	1.00	.322
SWEATING	0(0.0)	8(9.3)	11(12.1)	6(6.9)	25(7.1)	.003	.003	<.001	.013	.631	.590	.310
ASTHENIA	2(2.2)	8(9.3)	9(9.9)	4(4.6)	23(6.5)	.102	.055	.058	.441	1.00	.248	.250
DYSPEPSIA	6(6.7)	3(3.5)	6(6.6)	6(6.9)	21(5.9)	.743	.497	1.00	1.00	.498	.496	1.00
BACK PAIN	6(6.7)	7(8.1)	3(3.3)	3(3.4)	19(5.4)	.408	.779	.327	.497	.202	.211	1.00
ANOREXIA	1(1.1)	4(4.7)	10(11.0)	3(3.4)	18(5.1)	.028	.205	.009	.365	.164	.720	.082
VASODILATATION	2(2.2)	7(8.1)	6(6.6)	2(2.3)	17(4.8)	.158	.096	.278	1.00	.778	.099	.279
ABDOMINAL PAIN	2(2.2)	6(7.0)	4(4.4)	3(3.4)	15(4.2)	.457	.164	.682	.680	.527	.329	1.00
COUGH INCREASED	5(5.6)	3(3.5)	3(3.3)	4(4.6)	15(4.2)	.886	.720	.494	1.00	1.00	1.00	.716
LIBIDO DECREASED	1(1.1)	4(4.7)	7(7.7)	3(3.4)	15(4.2)	.163	.205	.064	.365	.537	.720	.331
VOMITING	1(1.1)	6(7.0)	5(5.5)	3(3.4)	15(4.2)	.203	.061	.211	.365	.762	.329	.721
MYALGIA	4(4.5)	4(4.7)	3(3.3)	3(3.4)	14(4.0)	.933	1.00	.719	1.00	.714	.720	1.00
NERVOUSNESS	2(2.2)	4(4.7)	5(5.5)	1(1.1)	12(3.4)	.355	.438	.444	1.00	1.00	.211	.211
AMBLYOPIA	1(1.1)	1(1.2)	6(6.6)	3(3.4)	11(3.1)	.159	1.00	.118	.365	.119	.621	.497
ANORGASMIA	0(0.0)	4(4.7)	4(4.4)	3(3.4)	11(3.1)	.174	.056	.121	.119	1.00	.720	1.00
ANXIETY	0(0.0)	4(4.7)	3(3.3)	4(4.6)	11(3.1)	.172	.056	.246	.058	.714	1.00	.716
PARESTHESIA	4(4.5)	1(1.2)	2(2.2)	4(4.6)	11(3.1)	.485	.368	.441	1.00	1.00	.368	.436
ACCIDENTAL INJURY	0(0.0)	5(5.8)	2(2.2)	3(3.4)	10(2.8)	.091	.027	.497	.119	.268	.496	.677
PHARYNGITIS	5(5.6)	2(2.3)	1(1.1)	2(2.3)	10(2.8)	.380	.444	.116	.444	.612	1.00	.615
ABNORMAL DREAMS	0(0.0)	2(2.3)	2(2.2)	5(5.7)	9(2.5)	.119	.240	.497	.028	1.00	.443	.270

(1) = PLACEBO, (2) = DLX20BID, (3) = DLX40BID, (4) = PRX20QD
*p-Values are from Fisher's Exact test.

Table HMATb.4. Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2 Percent
All Randomized Patients
Acute Therapy Phase (concluded)

	PLACEBO N=89 n(%)	DLX20BID N=86 n(%)	DLX40BID N=91 n(%)	PRX20QD N=87 n(%)	Total N=353 n(%)	p-Values* Overall	1vs2	1vs3	1vs4	2vs3	2vs4	3vs4
ABNORMAL EJACULATION	1(1.1)	2(2.3)	2(2.2)	4(4.6)	9(2.5)	.539	.616	1.00	.208	1.00	.682	.436
IMPOTENCE	0(0.0)	4(4.7)	2(2.2)	3(3.4)	9(2.5)	.165	.056	.497	.119	.434	.720	.677
TREMOR	1(1.1)	3(3.5)	2(2.2)	3(3.4)	9(2.5)	.682	.362	1.00	.365	.675	1.00	.677
FLATULENCE	1(1.1)	2(2.3)	1(1.1)	4(4.6)	8(2.3)	.424	.616	1.00	.208	.612	.682	.203
PALPITATION	2(2.2)	2(2.3)	2(2.2)	2(2.3)	8(2.3)	1.000	1.00	1.00	1.00	1.00	1.00	1.00
RASH	3(3.4)	1(1.2)	4(4.4)	0(0.0)	8(2.3)	.195	.621	1.00	.246	.369	.497	.121
TINNITUS	1(1.1)	4(4.7)	2(2.2)	1(1.1)	8(2.3)	.436	.205	1.00	1.00	.434	.211	1.00
NECK PAIN	0(0.0)	4(4.7)	3(3.3)	0(0.0)	7(2.0)	.031	.056	.246		.714	.059	.246
PRURITUS	2(2.2)	2(2.3)	1(1.1)	2(2.3)	7(2.0)	.881	1.00	.619	1.00	.612	1.00	.615
THINKING ABNORMAL	0(0.0)	1(1.2)	5(5.5)	1(1.1)	7(2.0)	.067	.491	.059	.494	.212	1.00	.211
TWITCHING	1(1.1)	3(3.5)	2(2.2)	1(1.1)	7(2.0)	.630	.362	1.00	1.00	.675	.368	1.00
URINARY FREQUENCY	0(0.0)	3(3.5)	2(2.2)	2(2.3)	7(2.0)	.398	.117	.497	.243	.675	.682	1.00

Table HMATb.5. Laboratory Data - Chemistry Analytes
Analytes with Statistically Significant Mean Change From Baseline to Endpoint Values
All Randomized Patients
Acute Therapy Phase

				Baseline		Change to Endpoint		p-Values	
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)	Pairwise*2
AST	U/L	PLACEBO	86	24.29	10.86	-2.05	10.11	.008	
		DLX20BID	81	22.68	7.44	3.17	10.60	(.475)	.001
		DLX40BID	81	22.67	10.21	1.25	8.03		.010
		PRX20QD	78	23.54	10.55	1.47	10.88		.015
ALT	U/L	PLACEBO	86	27.73	20.40	-3.56	13.73	.002	
		DLX20BID	81	25.48	15.69	4.15	18.93	(.480)	.004
		DLX40BID	81	24.37	17.50	3.86	13.69		<.001
		PRX20QD	78	28.51	20.92	-0.53	15.77		.070
CPK	U/L	PLACEBO	86	192.0	673.6	-55.6	427.5	.013	
		DLX20BID	81	126.6	89.0	30.9	115.1	(.813)	.040
		DLX40BID	81	123.8	101.5	-6.7	129.3		.599
		PRX20QD	78	111.0	63.8	31.8	173.0		.039
ALKPH	U/L	PLACEBO	86	68.6	20.4	-1.4	9.1	.049	
		DLX20BID	81	69.7	19.5	3.9	12.8	(.585)	.013
		DLX40BID	81	70.1	18.2	2.4	9.2		.019
		PRX20QD	78	72.5	23.4	0.9	14.0		.153
CALC	mmol/L	PLACEBO	86	2.397	0.111	-0.035	0.126	.009	
		DLX20BID	81	2.379	0.112	-0.006	0.148	(.280)	.273
		DLX40BID	81	2.398	0.120	-0.003	0.144		.193
		PRX20QD	78	2.357	0.102	0.032	0.110		<.001
SODIUM	mmol/L	PLACEBO	86	141.7	2.1	-1.2	2.8	.020	
		DLX20BID	81	141.5	2.2	-0.4	2.9	(.554)	.079
		DLX40BID	81	141.5	2.7	-0.2	3.3		.014
		PRX20QD	78	141.2	2.4	0.2	3.0		.004
UR AC	umol/L	PLACEBO	86	288.8	87.8	1.0	43.6	.145	
		DLX20BID	81	314.4	82.8	-1.0	48.8	(.810)	.262
		DLX40BID	81	304.9	84.1	-17.1	47.8		.022
		PRX20QD	78	300.8	81.5	-5.5	48.3		.150
T.BILI	umol/L	PLACEBO	86	6.8	6.0	0.9	2.9	.016	
		DLX20BID	81	6.7	4.2	-0.0	3.6	(.808)	.017
		DLX40BID	81	7.1	5.6	-0.5	3.4		.008
		PRX20QD	78	6.2	3.7	0.6	2.9		.591

Output stored as RMP.F1JO.HMAT.FINALB(LS604002)
Data from RMP.SAS.F1JM.MCHMATSW.STUDYB
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=investigator and treatment for the overall p-Value and model=investigator, treatment, and interaction for the interaction p-Value.
*2 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

Table HMATb.5. Laboratory Data - Chemistry Analytes
Analytes with Statistically Significant Mean Change From Baseline to Endpoint Values
All Randomized Patients
Acute Therapy Phase

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
CALC	CALCIUM
SODIUM	SODIUM
UR AC	URIC ACID
T.BILI	BILIRUBIN, TOTAL

Table HMATb.6. Laboratory Data - Nonchemistry Analytes
Analytes with Statistically Significant Mean Change From Baseline to Endpoint Values
All Randomized Patients
Acute Therapy Phase

				Baseline		Change to Endpoint		p-Values		
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)	Pair-wise*2	Model
HCT	1	PLACEBO	79	0.4189	0.0394	-0.0090	0.0278	.067		RDUC1
		DLX20BID	76	0.4237	0.0364	0.0011	0.0240	(.613)	.019	
		DLX40BID	76	0.4233	0.0350	-0.0007	0.0259		.067	
		PRX20QD	67	0.4201	0.0398	-0.0057	0.0263		.634	
MCHC	mml/L-Fe	PLACEBO	79	21.0	1.1	0.1	1.1	.225		RDUC1
		DLX20BID	76	21.0	0.8	-0.2	1.0	(.736)	.047	
		DLX40BID	76	21.0	1.0	0.0	1.1		.583	
		PRX20QD	67	21.0	1.0	0.0	1.2		.628	
WBC	GI/L	PLACEBO	80	7.43	1.76	-0.31	1.21	.043		RDUC1
		DLX20BID	76	7.24	1.83	0.18	1.76	(.053)	.085	
		DLX40BID	77	7.85	2.23	-0.44	1.64		.359	
		PRX20QD	69	7.60	1.99	0.08	1.92		.245	
BANDS	GI/L	PLACEBO	80	0.000	0.000	0.000	0.000	*		FULL3
		DLX20BID	76	0.000	0.000	0.000	0.000	(*)	*	
		DLX40BID	77	0.000	0.000	0.000	0.000		*	
		PRX20QD	69	0.000	0.000	0.000	0.000		*	
POLYS	GI/L	PLACEBO	80	4.565	1.391	-0.284	1.084	.074		RDUC1
		DLX20BID	76	4.514	1.411	0.140	1.604	(.345)	.143	
		DLX40BID	77	4.942	1.731	-0.340	1.498		.511	
		PRX20QD	69	4.709	1.590	0.144	1.679		.126	
BASO	GI/L	PLACEBO	80	0.046	0.027	0.004	0.037	.034		RDUC1
		DLX20BID	76	0.049	0.027	0.003	0.025	(.420)	.400	
		DLX40BID	77	0.051	0.029	0.007	0.028		.178	
		PRX20QD	69	0.055	0.031	-0.005	0.045		.140	
MCV	fL	PLACEBO	79	89.0	5.4	-0.9	4.1	.055		RDUC1
		DLX20BID	76	89.6	5.1	0.9	3.8	(.879)	.006	
		DLX40BID	76	89.3	4.9	0.1	3.9		.226	
		PRX20QD	67	89.7	4.5	0.0	4.7		.157	
U-SPGR	NO UNITS	PLACEBO	54	1.0194	0.0082	-0.0007	0.0080	.013		RDUC2
		DLX20BID	52	1.0175	0.0075	0.0012	0.0087	(.335)	.212	
		DLX40BID	51	1.0177	0.0073	0.0039	0.0071		.001	
		PRX20QD	47	1.0197	0.0077	0.0021	0.0088		.060	
TSH	mU/L	PRX20QD	2	0.835	0.021	0.165	0.148			
CK-MB	ng/ml	PLACEBO	1	17.30		-4.20				
CKMBRI	ngL/Uml	PLACEBO	1	0.30		0.20				

Table HMATb.6. Laboratory Data - Nonchemistry Analytes
Analytes with Statistically Significant Mean Change From Baseline to Endpoint Values
All Randomized Patients
Acute Therapy Phase (concluded)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL3 - *1 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=inv., treatment, and interaction.
*2 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=investigator and treatment for the overall p-Value and model=investigator, treatment, and interaction for the interaction p-Value.
*2 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

RDUC2 - *1 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=investigator and treatment for the overall p-Value and model=investigator, treatment, and interaction for the interaction p-Value.
*2 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
Note: At least one investigator does not have patients in every treatment group.

*Note: Error sum of squares is equal to 0, thus no p-Values are computed.

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
MCHC	MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
U-SPGR	UA-SPECIFIC GRAVITY
TSH	THYROID STIM. HORMONE
CK-MB	CK-MB (IMX)
CKMBRI	CK-MB RELATIVE INDEX

Table HMATb.7. Summary of Vital Signs and Weight Change from Baseline to Endpoint All Randomized Patients Acute Therapy Phase

	Treatment Group			
Variable	Placebo	Dulox 20	Dulox 40	Paroxetine
Heart rate (bpm)	n=86	n=84	n=87	n=85
Mean baseline (SD)	73.50 (8.40)	71.75 (11.04)	71.02 (8.10)	71.20 (9.75)
Mean change (SD)	-1.66 (8.47)	0.75 (10.02)	2.02 (9.86)	-0.21 (10.03)
p-value (active vs placebo)		.172	.044	.524
Systolic blood pressure (mmHg)	n=86	n=84	n=87	n=85
Mean baseline (SD)	119.57 (12.95)	117.30 (11.12)	120.62 (13.05)	119.76 (15.36)
Mean change (SD)	-3.24 (12.50)	0.13 (11.85)	-0.18 (12.51)	0.42 (12.53)
p-value (active vs placebo)		.176	.098	.052
Diastolic blood pressure (mmHg)	n=86	n=84	n=87	n=85
Mean baseline (SD)	75.60 (9.57)	75.49 (8.87)	77.94 (9.43)	77.18 (10.17)
Mean change (SD)	-0.47 (8.61)	2.11 (9.04)	0.20 (7.33)	0.34 (9.97)
p-value (active vs placebo)		.045	.563	.527
Weight (kg)	n=87	n=84	n=86	n=85
Mean baseline (SD)	80.61 (18.87)	82.08 (20.31)	83.16 (20.95)	89.77 (79.45)
Mean change (SD)	0.47 (1.95)	-0.02 (2.08)	-0.60 (2.20)	-0.41 (2.63)
p-value (active vs placebo)		.149	.002	.010

Abbreviations: Dulox 20 BID = duloxetine 20 mg twice daily; Dulox 40 BID = duloxetine 40 mg twice daily; n = number of patients; Parox 20 QD = paroxetine 20 mg once daily; SD = standard deviation.

Table HMATb.8. Treatment-Emergent Abnormal Electrocardiograms
All Randomized Patients
Acute Therapy Phase

Therapy	N	Abnormal ECG n(%)	Fisher's Exact Pairwise p-Values vs. 1)	vs. 2)	vs. 3)
1)PLACEBO	56	10(18%)			
2)DLX20BID	48	11(23%)	.626		
3)DLX40BID	52	10(19%)	1.00	.807	
4)PRX20QD	48	10(21%)	.804	1.00	1.00

Fisher's Exact p-value overall = 0.9436
Program: RMP.F1JSHMAT.SASPGM.STUDYB(FQECGB1B) QCA70
Data: RMP.SAS.F1JM.MCHMATSW.STUDYB

Table HMATb.9. Summary of Arizona Sexual Experiences Scale
Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase

	Treatment Group			
Variable	Placebo	Dulox 20	Dulox 40	Paroxetine
ASEX Total Score	n=49	n=50	n=45	n=48
Mean baseline (SD)	16.20 (5.06)	15.90 (4.10)	16.36 (3.90)	15.96 (4.74)
Mean change (SD)	0.02 (3.94)	0.50 (3.88)	0.62 (4.80)	0.56 (5.13)
LS Means p-value (active vs placebo)		0.496	0.553	.728
ASEX sum of items 1 and 2	n=85	n=80	n=83	n=72
Mean baseline (SD)	7.53 (2.78)	7.55 (2.45)	7.58 (2.02)	7.60 (2.58)
Mean change (SD)	0.13 (2.06)	-0.24 (2.19)	0.02 (2.07)	-0.10 (2.29)
LS means p-value (active vs placebo)		.277	.850	.667

Abbreviations: ASEX = Arizona Sexual Experiences Scale; Dulox 20 BID = duloxetine 20 mg twice daily; Dulox 40 BID = duloxetine 40 mg twice daily; n = number of patients; Parox 20 QD = paroxetine 20 mg once daily; SD = standard deviation.

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Differences in Reporting Serious Adverse Events in Industry Sponsored Clinical Trial Registries and Journal Articles on Antidepressant and Antipsychotic Drugs – A Cross-sectional Study

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Differences in Reporting Serious Adverse Events in Industry Sponsored Clinical Trial Registries and Journal Articles on Antidepressant and Antipsychotic Drugs - A Cross-sectional Study

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ABSTRACT

Objective: To examine the degree of concordance in reporting serious adverse events (SAEs) from antidepressant and antipsychotic drug trials among journal articles and clinical trial summaries, and to categorize types of discrepancies.

Design: Cross-sectional study of summaries of all antidepressant and antipsychotic trials included in an online trial registry and their first associated stand-alone journal articles.

Setting: Clinicalstudyresults.org, sponsored by Pharmaceutical Research and Manufacturers of America; clinicaltrials.gov, administered by the US National Institutes of Health.

Main outcome measure: Three coders extracted data on the numbers and types of SAEs.

Results: 244 trial summaries for six antidepressant and antipsychotic drugs were retrieved, 142 (58.2%) listing an associated article. Of 1,608 SAEs in drug-treated participants according to trial summaries, 694 (43.2%) did not appear in associated articles. Nearly 60% of SAEs counted in articles and 41% in trial summaries had no description. Most cases of death (62.3%) and suicide (53.3%) were not reported in articles. Half or more of the 142 pairs were discordant in reporting the number (49.3%) or description (67.6%) of SAEs. These discrepancies resulted from journal articles' 1) omission of complete SAE data, 2) reporting acute phase study results only, and 3) more restrictive reporting criteria. Trial summaries with zero SAE were 2.35 (95% confidence interval, 1.58 to 3.49; P<0.001) times more likely to be published with no discrepancy in their associated journal article. Since clinicalstudyresults.org was removed from the Internet in 2011, only 7.8% of retrieved trial summaries appear with results on clinicaltrials.gov.

Conclusions: Substantial discrepancies exist in SAE data found in journal articles and registered summaries of antidepressant and antipsychotic drug trials. Two main scientific sources accessible to clinicians and researchers are limited by incomplete, ambiguous, and inconsistent reporting. Access to complete and accurate data from clinical trials of drugs currently in use remains a pressing concern.

ARTICLE SUMMARY

Strengths and limitations of this study

- Published journal articles from antidepressant and antipsychotic drug trials report substantially fewer serious adverse events than associated clinical trial summaries posted by industry trial sponsors on a previously active online registry.
- Our findings of inconsistencies and ambiguities in serious adverse event reporting in both journal articles and trial summaries suggest that registries might not provide meaningfully improved access to complete and transparent clinical trial data.
- The registry from which we retrieved trial summaries has since been removed from the Internet and most trial summaries were not transferred with results to clinicaltrials.gov, making our analysis a unique examination of data that has been lost or scattered.
- We examined only the first stand-alone journal article associated with each trial summary, so it is possible that additional harms outcomes and longer-term outcomes absent from our sample of journal articles were reported in subsequent articles. Nevertheless, clear trends of incomplete reporting were apparent between journal article and trial summary sources.

INTRODUCTION

Publication bias and concerns regarding the integrity of the medical treatment knowledge base have led to various mechanisms, such as publicly accessible clinical trial registries, to promote transparent and complete reporting of clinical trial results [1, 2]. As the next most accessible source of drug information after published articles, clinical trial summaries available in online trial registries might contribute to improved evidence synthesis since they are supposed to provide an inclusive synopsis of both positive and negative results [3, 4]. In this study we compare serious adverse events (SAEs) found in industry-funded antipsychotic and antidepressant drug trial summaries posted by trial sponsors on an online trial registry, with SAEs found in published journal articles reporting on the same trials.

SAEs by definition result in death, hospitalization or significant disability and are therefore particularly important to report from a clinical trial because of their potential impacts on treatment decision-making and patient safety. International Conference on Harmonization (ICH) guidelines state that SAEs "deserve special attention" relative to other types of adverse effects, including providing individual-level patient detail and narrative for each SAE in clinical trial reports submitted to regulatory agencies [5]. Regulatory agencies in the United States and across Europe require trial sponsors to immediately report unexpected or life-threatening SAEs [6, 7]. However, the extent to which SAEs are then reported in outlets for clinicians, researchers, and the public is unknown, though evidence suggests incomplete and ambiguous reporting of harms-related data [8-10]. Recent settlements resulting from state and federal lawsuits in the United States against pharmaceutical manufacturers for minimizing or concealing drug harms, further highlight the need for increased diligence in discerning what important harm-related drug information might remain unknown or distorted in scientific outlets for reporting clinical trial

results [11-13]. While previous research has demonstrated that harms data are less completely reported in journal articles than clinical trial summaries, these studies provide primarily quantitative counts of reporting practices [8-10]. The present analysis seeks to elaborate the nature of quantitative and qualitative differences in SAE reporting, and possible explanations for reporting discrepancies.

Antipsychotic and antidepressant drugs — which rank among the 10 highest-selling drug classes in the U.S. and the world [14, 15] — are mainstay treatments in psychiatry and prescribed for myriad indicated and off-label, psychiatric and non-psychiatric uses [16, 17]. Journal publications, clinical trial summaries posted on trial registries, and data from regulatory agencies such as the U.S. Food and Drug Administration (FDA) currently represent the primary information sources for clinicians and decision-makers regarding the safety and effectiveness of drug treatments. In contrast to substantially lengthier accounts of trials found in clinical study reports submitted to regulatory agencies, clinical trial summaries are abbreviated, concise descriptions of trials' background, methodology, and positive and negative results. Similar to clinical study reports, they are structured according to templates described in the ICH *Guidelines for Industry: Structure and Content of Clinical Study Reports* [5], though their level of detail can vary substantially. Using the clinical trial summaries for all trials of these drugs posted by industry sponsors on clinicalstudyresults.org, we aimed to 1) count and describe SAEs reported in trial summaries and, as applicable, their associated peer-reviewed journal articles, 2) assess the consistency of SAE reporting between pairs of trial summaries and associated journal articles, and 3) categorize possible explanations for discrepant reporting.

METHODS

Data Sources

Clinical trials summaries were retrieved from clinicalstudyresults.org, the former online public registry sponsored by the Pharmaceutical Research and Manufacturers of America (PhRMA). Published journal articles were identified using the bibliography listed on the cover page of each trial summary.

2.1.1 Clinical trial summaries

The clinicalstudyresults.org registry was established in 2005 by PhRMA as a single repository for pharmaceutical manufacturers to post result summaries of their sponsored clinical trials. At the time, the federally funded clinicaltrials.gov, established in 2000 and administered by the U.S. National Institutes of Health, required manufacturers to register only the existence of their trials. According to PhRMA guidelines, complete results of all hypothesis-testing clinical trials completed after 2002 for products approved for marketing in the United States were to be submitted to its registry within one year after completion of the trial, and references to articles published in peer-reviewed journals added to the trial summary as soon as they were published [18].

In May 2011, we retrieved all Phase II, III, and IV clinical trial summaries (n=329) for all nine drugs within the antidepressant and antipsychotic classes listed on clinicalstudyresults.org. We excluded three drugs (desvenlafaxine, quetiapine, and venlafaxine) with registered trials but no or few posted trial summaries. For the remaining six drugs (n=254 trial summaries) we retained the summaries with trial completion dates on or before 2008, allowing at least 2.5 years for a trial to reach publication in the peer-reviewed literature (see Appendix Table 1). This resulted in 244 (74%) clinical trial summaries for six drugs from three manufacturers: aripiprazole (Abilify, Bristol-Myers Squibb), atomoxetine (Strattera, Eli Lilly), duloxetine (Cymbalta, Eli Lilly), olanzapine (Zyprexa, Eli Lilly), sertraline (Zoloft, Pfizer), and

ziprasidone (Geodon, Pfizer). Trial summaries averaged 18 pages in length (range: 3 to 147). Supplementary File 1 provides a trial summary illustrating the typical format of the documents in this sample. Trial summaries include both pre-marketing studies that were sent to regulatory agencies for drug approval and post-marketing studies for new indications, additional outcomes, and long-term follow-up.

Journal articles

We used the bibliography listed on the cover page of each trial summary to retrieve the earliest journal article reporting on the full trial. We emailed and telephoned the medical communications, clinical trials, or customer relations department of each manufacturer of the included drugs to inquire about the completeness of the list of trial summaries and journal articles posted on clinicalstudyresults.org. No representative from any manufacturer could confirm completeness of the posted lists nor provide a current list of all clinical trials and journal publications for the respective drugs. Representatives directed us to visit clinicaltrials.gov to view current and completed trials, and PubMed for a list of publications. We then attempted to manually search PubMed to match possible additional publications with the trial summaries, but the absence of trial identification numbers in journal articles made it extremely difficult to crosscheck and match all sources reliably. These additional efforts, therefore, did not affect the final sample size.

Data Extraction

We employed double data extraction. One coder extracted the number and exact description of SAEs reported to occur in drug-treated participants from the *Results* section of each trial summary and journal article. For multi-phase trials, we tallied the SAEs occurring in each phase. The number of patients experiencing SAEs was counted in the few cases where the

number of events was not provided, therefore underestimating the actual number of SAEs. We also extracted from each source the trial start and completion year, article publication date, study length, sample size, targeted indication, and consistency of reporting SAEs (see explanation below). A second coder independently extracted these data from a 50% random sample of trial summaries and articles for three of the six drugs. A third coder repeated the same process for the other three drugs. The values obtained by the second and third coders were compared to those obtained by the first. Any discrepancies were resolved by consensus. Coding for most reports and articles was straightforward and few disagreements in recordings between coders were found.

We evaluated the consistency of the number and description of SAEs occurring in drug-treated participants reported between each trial summary and its associated article. The *number* of SAEs was considered inconsistent if (1) reported numbers differed between the two sources (e.g., aripiprazole trial CN138-008: trial summary cited 7, journal article 6, SAEs), (2) one source reported the number of SAEs while the other contained no or an ambiguous statement about their occurrence; or (3) the journal article did not report the trial phase in which SAEs did occur according to the trial summary (e.g., ziprasidone trial 1006: in a 60-week multi-phase study with 8 SAEs reported in the summary, the article reports findings from the 8-week acute phase with zero SAEs). The *description* of SAEs was considered inconsistent if only one source described the events (e.g., duloxetine trial 6091: the summary describes 1 SAE as an intentional overdose, the article omits the description but accurately reports the number), or if one source less completely described the events than the other source (e.g., duloxetine trial 8601: the summary lists one death from suicide as well as other SAEs related to psychiatric worsening, but the article mentions only the suicide). Sources were considered consistent if both reported the

number or description of SAEs identically, or if neither reported such information. In each instance of discrepant reporting, we performed an in-depth inductive analysis involving a careful review of the trial summary and journal article to identify a possible explanation for the discrepancy. We then grouped the emerging patterns, which resulted in three categories (described in the results section): differences in study length or phase reported, differences in reporting criteria used, and apparent selective reporting of SAE data. Discrepancies were only assigned to the latter category after ruling out the other two explanations. No additional categories to explain discrepant reporting emerged from the analysis.

Analysis

We used descriptive statistics to summarize quantitative variables related to study characteristics and frequencies for categorical variables. We calculated the number of SAEs per patient treated for each drug by dividing the number of SAEs reported in trial summaries and journal articles, respectively, by the total number of drug-treated participants.

We extracted exact descriptions of SAEs and then categorized them as: behavioral or cognitive, physical, no description provided, and unspecified (including overdose, dependence, death or hospitalization for unspecified reasons, and accidental injury). We further counted the number of SAEs reported as death, suicide, suicide attempt, homicidal ideation, and new or worsened psychiatric symptoms.

We calculated risk ratios to test the likelihood of trial summaries reporting zero SAEs to be published as stand-alone journal articles in a manner congruent with the summaries, compared to trial summaries reporting ≥ 1 SAEs. Risk ratios were calculated with 95% confidence intervals and Pearson's chi-square analysis using PASW Statistics, version 18 software [19].

RESULTS

Search Results and Sample Selection

Using the bibliography listed on the cover page of each trial summary, we counted a total of 496 listed publications (an average of two publications per trial, with an average time to publication of 2.5 years), from which we retrieved the earliest journal article reporting on the full trial. From the total we excluded 261 (52.6%) sub-set analyses (i.e., reports on a sub-set of the total sample based on a shared characteristic, such as gender), meta-analyses, and conference abstracts. Of the 244 trial summaries, 72 (29.5%) listed no publication of any kind, 30 (12.3%) listed only one or more of the excluded publication types, and 142 (58.2%) listed at least one associated stand-alone journal article (see Figure 1). The final sample consisted of 142 trial summary-journal article pairs listed on clinicalstudyresults.org and an additional 102 trial summaries from the registry with no associated journal article.

Sample Description

For each of the six drugs included in this analysis, Table 1 summarizes trial characteristics as reported in trial summaries, their associated journal articles, and the additional trial summaries having no associated journal article (referred to as *unpublished trial summary* on all tables and appendices). Overall, a stand-alone journal article was available for 58.2% of trials in this sample, though this varied by drug from a low of 27.6% for trials of ziprasidone to 72.9% for trials of duloxetine. Journal articles reported findings for an identical or nearly identical number of participants as their associated trial summaries. The 102 unpublished summaries, however, included data on an additional 20,084 drug-treated participants. The median study length was shorter in journal articles (11 weeks) than in their paired trial summaries (12 weeks) or unpublished trial summaries (16 weeks).

The three antipsychotic drugs (n=129 trial summaries) were being tested for the treatment of psychotic disorders (56.6% of studies), bipolar disorder or mania (26.4%), or other conditions (16.2%) such as depressive disorders, Alzheimer's, autism, alcohol dependence, or borderline personality disorder. The three antidepressant drugs (n=115 trial summaries) were being studied for the treatment of attention deficit hyperactivity disorder (42.6%), depressive disorders (34.8%), anxiety disorders (8.7%), or other conditions (14%) such as pain-related disorders or post-traumatic stress disorder.

Serious Adverse Events in Trial Summaries

Ninety percent of all trial summaries (n=244) reported a precise number of SAEs occurring in the trial. The 142 trial summaries with an associated journal article reported 1,608 SAEs, and the 102 trial summaries with no associated journal article reported an additional 1,423 SAEs. Table 2 details the total and per patient numbers of SAEs reported in trial summaries for each drug. Appendix Table 2 lists additional SAEs for the 10 excluded trial summaries with trial completion dates in 2009 or later.

No description was provided for 41% of the SAEs cited in trial summaries (46% and 20% of SAEs in antipsychotic and antidepressant trials, respectively). An additional 11.6% of SAEs were non-specifically described, such as "accidental injury" in duloxetine trial 1126. When a specific description was present, we categorized 28.4% of SAEs as behavioral or cognitive and 18.9% as physical. Table 3 details all cases of death, suicide, and new or worsened psychiatric symptoms for each drug.

Serious Adverse Events in Journal Articles

Nearly 40% of journal articles failed to specify the number of SAEs that occurred in the trial (Table 2), containing either no statement related to SAEs or an ambiguous statement without

an actual number of SAEs, such as sertraline trial 1060: "no subjects had serious adverse events related to study treatment." A total of 914 SAEs were reported across the 85 journal articles that did include specific data on SAE occurrence.

Most SAEs (58.9%) reported in journal articles (61% in antipsychotic and 55.5% in antidepressant trials) had no accompanying description and another 8% were non-specifically described. Nearly one-fifth (18.9%) of SAEs were behavioral or cognitive in nature and 14.6% were described as physical. Table 3 shows that one-quarter of SAEs described in journal articles were categorized as death, suicide, homicidal ideation, or new or worsened psychiatric symptoms.

Consistency of Reporting in Trial Summary-Journal Article Pairs

Just over half (56.8%) of the 1,608 SAEs experienced by drug-treated participants according to trial summaries (n=142) were also reported in associated journal articles. This proportion varied widely between the drugs, from 14.8% of SAEs in atomoxetine trials to 114.6% in aripiprazole trials (see Table 2). The number of SAEs per patient for most drugs were lower in articles (0.03, range: 0.003 - 0.07) than in associated summaries (0.05, range: 0.02 – 0.13). Trial summaries with no associated article averaged the highest number of SAEs per patient (0.07, range: 0.01 – 0.14).

Half or more of the 142 trial summary-journal article pairs were discordant in reporting the number (49.3%) or description (67.6%) of SAEs (Table 4). In half of these pairs, the reported number of SAEs differed by more than 20% between the two sources.

Both journal articles and associated trial summaries failed to describe a substantial proportion of SAEs. Most cases of death (62.3%) and suicide (53.3%) cited in trial summaries were not reported in associated journal articles (Table 3).

The 34 trial summaries with zero SAEs were 2.35 (95% confidence interval, 1.58 to 3.49; P<0.001) times as likely to have an associated journal article reporting this data consistently with the trial summary data as were the 181 summaries with 1 or more SAEs.

Explanations for Discrepant Reporting

Seventy (49.3%) of the 142 trial summary-journal article pairs were discrepant in SAE reporting. Half of these instances might be explained by differences between sources in the study length or phase being reported (25%, 18/70) or in the reporting criteria used (25%, 18/70). Table 5 provides examples of each of these forms of discrepant reporting. Importantly, while some journal articles appeared to apply more restrictive reporting criteria that might lead to omitting certain data, the many articles that did report exact SAE numbers often did so regardless of presumed causality to the study drug. For example, articles and summaries for olanzapine trials 3131 and 7031 reported all SAEs even though some events were thought to be unrelated to the study drug. Yet, the article for olanzapine trial 4414 separately details SAEs thought to be related and unrelated to the drug [20]. Thus, no clear or consistent pattern on SAE reporting criteria emerged from this sample of journal articles.

Another one-third (34.3%, 24/70) of discrepancies appear to be simple failures of journal articles to report complete SAE data (see Table 5). In a minority (14.3%, 10/70) of cases, however, the journal article provided more precise data or a higher number of SAEs than the trial summary. The article for aripiprazole trial CN138-050, for example, cites 6 SAEs in drug-treated participants [21], while the summary states only that the incidence of SAEs was low.

Post Hoc Analysis of Clinical Trial Summaries on Clinicaltrials.gov

In December 2011, clinicalstudyresults.org was removed from the Internet for unknown reasons. The Internet archive for the website (found here: Internet archive) suggests that the

expansion of other registries made clinicalstudyresults.org seem redundant from industry's perspective [22]. One year after this removal of the registry, we cross-checked our data source by searching for each of the 244 trial summaries on clinicaltrials.gov. (In that database, the U.S. Food and Drug Administration Amendment Act [FDAAA] of 2007 newly mandated trial sponsors to include summary reporting of results for trials that were initiated after or ongoing as of late 2007.) Our search revealed that 139 (57%, range across drugs: 25% - 80%) of the 244 trials were registered on clinicaltrials.gov, but only 15 of these (10.8%, range across drugs: 0% - 39%) had posted study results. In October 2013, nearly two years after the clinicalstudyresults.org takedown, these numbers had only slightly budged, with 19 registered trials now reporting study results. While nearly all (99%) of the trial summaries not currently registered on clinicaltrials.gov have trial start or completion dates prior to 2007, 75% of trial summaries that *are* registered on the website also have pre-2007 trial dates. In the interest of openness and transparency, we created a publicly accessible website (www.rxarchives.com) where all 244 trial summaries are posted in pdf format and freely available for download.

DISCUSSION

This study demonstrates that a substantially lower number of SAEs appear in published journal articles than registered trial summaries of antidepressant and antipsychotic drug trials, and shows further that both sources for drug information are often inconsistent or ambiguous in SAE reporting. In this study, 43.2% of all SAEs appearing in 142 trial summaries posted on an online registry across six psychotropic drugs were not reported in the first associated stand-alone journal articles listed by the drug's manufacturer. Failure to describe the nature of SAEs was also common in both sources. Given that many consumers of psychotropic drugs take these medications for months or years, that approximately one-quarter of journal articles reported only

acute phase results of longer-term trials and that the median study length in trial summaries with an associated journal article (12 weeks) was four weeks shorter than in trials without a journal article highlight an additional attrition of evidence on longer term outcomes.

These findings are congruent with other recent analyses demonstrating more complete outcomes information in registered clinical trial summaries compared to published journal articles [9], although examination of full clinical study reports reveals that both of the latter sources suffer from incomplete reporting of key data [10]. Similar to our results, Riveros and colleagues [9] found that registered trial summaries (99%; present study 90%) more often report data on serious adverse events compared to published articles (63%; present study 60%). However, in an analysis comparing publicly available data in registered clinical trial summaries and journal publications to full clinical study reports submitted to a regulatory agency for drug products, the former sources reported complete information on harms outcomes significantly less (~25%) than clinical study reports (87% of harms outcomes reported completely) [10]. SAEs, specifically, were reported completely only 51% of the time in journal articles and trial summaries, and 30% of SAE outcomes were not reported at all in these sources. In their analysis of full clinical study reports on the influenza drug Tamiflu, Doshi, Jefferson, and Del Mar [3] are alarmed by the important data remaining unknown to most physicians when clinical trial information is limited to the published journal literature. The occurrence of SAEs and the rationales for classifying events as adverse are among many possible discoveries in clinical study reports that can markedly alter a drug's benefit-to-risk profile. While publication bias of this sort in the literature has long been acknowledged or suspected [23-25], the present study clarifies the degree to which such bias distorts the perception of important harms outcomes (i.e., number and nature of SAEs) across two classes of popularly used psychotropic drugs. Also, this study adds to

the evidence base questioning whether information posted in online clinical trial registries represents meaningful improvement.

For another 102 trials with no associated stand-alone journal article in the present study, the clinical trial summaries report an additional 1,423 SAEs and represent the only publicly available data source on these trials. In a recent examination of 585 large randomized trials registered on clinicaltrials.gov, 29% had no associated journal publication and most (78%) of those also had no results available on the clinicaltrials.gov registry [26]. Riveros and colleagues [9] found that 50% of 594 randomly sampled controlled drug trials on clinicaltrials.gov had no corresponding published article. These findings highlight the necessity for clinicians, researchers, and decision-makers to consult multiple sources in order to achieve a comprehensive and more complete appraisal of drugs' safety profile, although again, clinical trial summaries are themselves limited by incomplete reporting [10, 27] and by regulatory policies that require registration of only recent [1] or new trials [28].

Our post hoc analysis further revealed that, while 57% (139/244) of the present sample of trial summaries are registered on clinicaltrials.gov, only 7.8% (19/244) are available on the registry with results. Three-quarters of these currently registered trials have trial start or completion dates prior to 2007, thereby suggesting that actual registration practices on clinicaltrials.gov may be more inclusive than the minimum requirements set out by the FDAAA. Access to the full evidence base of drugs currently in use, including recent studies and those conducted prior to widespread deployment of registries, is essential for sound treatment decision-making and the assurance of present day patient safety [10, 29], but the important efficacy and harms information contained in these 225 trials on six psychotropic drugs has been lost or scattered. As of this writing, Pfizer (sertraline and ziprasidone) and Bristol-Myers Squibb

(aripiprazole) company websites include trial summaries or links to clinicaltrials.gov only for trials completed or ongoing as of 2007, in accordance with FDAAA guidelines. All clinical trial summaries included in the present analysis for atomoxetine, duloxetine, and olanzapine are available on Eli Lilly's company website. Some data, then, have been lost to the evidence base with the removal of clinicalstudyresults.org, while other data are still available but no longer accessible through a single repository. The important harms data contained in the present body of trial summaries provides further support for the recommendation that all ongoing, recent, and archive drug trials for all new and existing drugs be made available to clinicians and consumers in a clear and accessible format, including links between all trial-related documents (journal articles, registry records, trial protocol, and so on) for transparent navigation of each trial component to the core study [10, 30, 31].

The present study has important limitations and strengths. First, although participating industry trial sponsors had posted on their respective websites statements of their commitment to posting all trial results in a timely manner on clinicalstudyresults.org, the completeness and accuracy of trial summaries on clinicalstudyresults.org could not be verified. However, since our crosscheck of summaries on clinicaltrials.gov revealed that few of these trials were transferred with results, our present analysis provides a glimpse on unique trial evidence that a contemporary standard database fails to capture. Second, only the first stand-alone journal article for each trial was included in this analysis. For trials with multiple publications, additional information on SAEs might appear in subsequent articles. However, this possibility might be slight as the median number of journal articles per trial summary was one, and over half of total articles listed for the six drugs were pooled or sub-set analyses or conference abstracts. We do not know whether the trends observed in the 142 trial summary-journal article pairs would hold

for the other 102 trials. Finally, the results of this study cannot be generalized to other drugs and drug classes, but do add to the substantial body of empirical findings demonstrating poor adverse event assessment and reporting practices and a distortion of evidence through selective reporting of industry-sponsored psychotropic drug research [24, 32-35].

The integrity of the medical treatment knowledge base preserves sound clinical practice and ensures patient safety. If nearly half of serious adverse events in psychotropic drug research are not reported in journal articles and many more can be found in sources not easily accessed by relevant treatment decision-makers [3, 10, 36], then, without integrating multiple data sources, benefit-to-harm assessments made by groups constructing clinical guidelines and by individual clinicians making prescription decisions are based on incomplete evidence and likely biased toward underestimating risks. Multiple solutions to the grave problem of incomplete reporting of clinical trials have been proposed, and some recent strides have been made. Some suggest shifting toward public funding and control of drug research in order to produce credible information accessible and transparent to all stakeholders [37-40]. Some propose to treat failures to disclose complete knowledge of adverse effects from clinical trials as criminal offenses requiring criminal prosecution of responsible individuals and companies [41]. At the same time, ongoing campaigns have gained momentum across the United Kingdom in calling for pharmaceutical manufacturers to share clinical study reports on all drugs in use [31] and in the United States for sharing clinical trial datasets with independent scientists [42]. Many agree, however, that regulatory requirements for registering new and ongoing studies does not adequately protect the millions of patients currently taking prescription drugs [10, 31], and the pharmaceutical industry has been slow and resistant to accepting the level of openness that scientists and the public have been calling for [31, 43].

The present findings highlight inconsistencies in harms-related reporting between published articles and trial registry summaries of psychotropic drugs, and indicate that clinical decisions regarding drug use may be based on substantially truncated evidence. Policy discussions in this area should consider to what extent patients who use drugs, clinicians who prescribe drugs and the public who finance most of their use deserve access to complete and accurate scientific data from drug trials.

Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; 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.

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Contributors: SH and DC conceived the idea of the study and were responsible for the design of the study. SH and RJ were responsible for the acquisition of the data, for undertaking data coding and analysis, and produced the tables. DC also contributed to data coding, and provided critical input into the analysis and interpretation of results. The initial draft of the manuscript was prepared by SH and then circulated repeatedly among all authors for critical revision.

Data Sharing: All clinical trial summaries that were analysed in this study have been uploaded by the first author (S.H.) to a publicly-accessible website (www.rxarchives.com) for download.

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Table 1. Description of included studies

	N	Modal trial completion or article publication year	Average (median) number of publications per trial[a]	Average years from trial completion to article publication	Average (median) trial length in weeks	Maximum trial length in weeks	Number of drug treated participants (% as reported in summaries)	Total no. participants
Aripiprazole								
Trial summary	28	2006	0.62 (1)	2.6	20.8 (8)	140	5,809	9,935
Journal article	28	2009	--	--	10.7 (8)	52	5,696 (98)	9,728
Unpublished trial summary[b]	21	2003	--	--	29.9 (26)	94	6,896	8,112
Olanzapine								
Trial summary	33	2000	1.78 (1)	2.7	26.5 (24)	78	8,515	12,136
Journal article	33	2002	--	--	16.8 (6)	78	8,225 (97)	11,932
Unpublished trial summary	18	2005	--	--	18.7 (19)	48	3,120	4,997
Ziprasidone								
Trial summary	8	2005	0.79 (0)	3.8	17.1 (12)	60	910	1,399
Journal article	8	2007	--	--	10.5 (10)	27	910 (100)	1,399
Unpublished trial summary	21	2008	--	--	38.4 (12)	320	3,268	4,459
Atomoxetine								
Trial summary	31	2005	1.76 (1)	2.2	35.9 (18)	181	4,313	7,094
Journal article	31	2007	--	--	16.7 (10)	97	4,138 (96)	6,975
Unpublished trial summary	20	2006	--	--	35.7 (24)	104	3,640	4,469
Duloxetine								
Trial summary	35	2005	4.69 (3)	2	27.1 (13)	103	14,185	18,334
Journal article	35	2007	--	--	22.8 (13)	103	14,185 (100)	18,334
Unpublished trial summary	13	2004	--	--	24.2 (15)	62	2,115	3,413
Sertraline								
Trial summary	7	2003	1.53 (1)	2.9	37.7 (22)	128	2,147	2,326
Journal article	7	2005	--	--	22.9 (22)	52	2,147 (100)	2,326
Unpublished trial summary	9	2001	--	--	15.4 (10)	36	1,045	1,541
All Drugs								
Trial summary	142	2005	2 (1)	2.5	27.8 (12)	181	35,879	51,224
Journal article	142	2007	--	--	16.7 (11)	103	35,269 (98)	50,694
Unpublished trial summary	102	2006	--	--	28.8 (16)	320	20,084	26,992

[a]Average and median number of publications reflect all publications listed on the trial summary cover page, including stand-alone journal articles, meta-analyses, sub-set analyses, and conference abstracts.
[b]Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

Table 2. Number of serious adverse events (SAEs) reported in trial summaries and journal articles for drug-treated participants

	Number (%) of studies that report the number of SAEs[a]	Number of SAEs (% as reported in associated trial summaries)	Number of SAEs per patient treated[b]
Aripiprazole			
Trial summary (n=28)	26 (92.9)	364	0.06
Journal article (n=28)	27 (96.4)	417 (114.6%)	0.07
Unpublished trial summary[c] (n=21)	20 (95.2)	504	0.07
Olanzapine			
Trial summary (n=33)	28 (84.8)	544	0.06
Journal article (n=33)	11 (33.3)	66 (12.1%)	0.008
Unpublished trial summary (n=18)	17 (94.4)	302	0.10
Ziprasidone			
Trial summary (n=8)	7 (87.5)	117	0.13
Journal article (n=8)	5 (62.5)	53 (45.3%)	0.06
Unpublished trial summary (n=21)	21 (100.0)	446	0.14
Atomoxetine			
Trial summary (n=31)	25 (80.6)	88	0.02
Journal article (n=31)	14 (45.2)	13 (14.8%)	0.003
Unpublished trial summary (n=20)	17 (85.0)	35	0.01
Duloxetine			
Trial summary (n=35)	32 (91.4)	453	0.03
Journal article (n=35)	27 (77.1)	349 (77%)	0.02
Unpublished trial summary (n=13)	12 (92.3)	117	0.06
Sertraline			
Trial summary (n=7)	7 (100.0)	42	0.02
Journal article (n=7)	2 (28.6)	16 (38.1%)	0.007
Unpublished trial summary (n=9)	8 (88.9)	19	0.02
All Drugs			
Trial summary (n=142)	125 (88.0)	1,608	0.05
Journal article (n=142)	85 (59.9)	914 (56.8%)	0.03
Unpublished trial summary (n=102)	95 (93.1)	1,423	0.07

[a]The figures in this column indicate those publications that reported the number of SAEs that occurred. Some publications contained no statement about the occurrence of SAEs or contained an ambiguous statement without specifying the actual number of SAEs, such as "No SAEs thought to be related to study medication occurred."
[b]The numerator equals the number of events; the denominator equals the total number of drug-treated participants, as reported in Table 1.
[c]Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

Table 3. Number of deaths, suicide- and homicide-related events, and psychiatric serious adverse events in drug-treated participants

	Death	Suicide, completed	Suicidal ideation, attempts, injury	Homicidal ideation	New or worsened psychiatric symptoms	Total
Aripiprazole						
Trial summary (n=28)	79	1	4	0	79	163
Journal article (n=28)	27 (34.2)[a]	1 (100.0)	5 (125.0)	0	66 (83.5)	99 (60.7)
Unpublished trial summary[b] (n=21)	15	1	10	0	92	118
Olanzapine						
Trial summary (n=33)	50	9	18	0	85	162
Journal article (n=33)	19 (38.0)	1 (11.1)	4 (22.2)	0	14 (16.5)	38 (23.5)
Unpublished trial summary (n=18)	7	3	21	1	95	127
Ziprasidone						
Trial summary (n=8)	0	1	13	1	30	45
Journal article (n=8)	0 (0)	1 (100.0)	5 (38.5)	1 (100.0)	14 (46.7)	20 (44.4)
Unpublished trial summary (n=21)	18	1	23	3	141	186
Atomoxetine						
Trial summary (n=31)	0	0	7	0	6	13
Journal article (n=31)	0	0	0 (0)	0	0 (0)	0 (0)
Unpublished trial summary (n=20)	1	0	5	0	5	11
Duloxetine						
Trial summary (n=35)	11	4	40	0	27	82
Journal article (n=35)	11 (100.0)	4 (100.0)	33 (82.5)	0	21 (77.8)	69 (84.1)
Unpublished trial summary (n=13)	3	0	10	0	20	33
Sertraline						
Trial summary (n=7)	11	0	5	0	11	27
Journal article (n=7)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)
Unpublished trial summary (n=9)	1	0	10	1	4	16
All Drugs						
Trial summary (n=142)	151	15	87	1	238	492
Journal article (n=142)	57 (37.7)	7 (46.7)	47 (54.0)	1 (100.0)	115 (48.3)	227 (46.1)
Unpublished trial summary (n=102)	45	5	79	5	357	491

[a]Percent as reported in associated trial summaries.
[b]Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

Table 4. Percentage of trial summary -journal article pairs that report serious adverse event (SAE) data consistently across sources

Summary-Article Pairs	Number of SAEs		Description of SAEs
	Consistent across sources	> 20% difference across sources	Consistent across sources
Aripiprazole (n=28)	67.9	25.0	28.6
Olanzapine (n=33)	27.3	72.7	30.3
Ziprasidone (n=8)	37.5	37.5	37.5
Atomoxetine (n=31)	54.8	45.2	42.0
Duloxetine (n=35)	62.9	37.1	31.4
Sertraline (n=7)	28.6	71.4	14.3
All Drugs (n=142)	50.7	49.2	32.4

Table 5. Explanations for Discrepant Reporting of SAEs between Journal Articles and Trial Summaries

General explanation for discrepant reporting	Specific explanation for discrepant reporting	Example
Difference in study length or phase reported	Reporting only one phase of a multi-phase trial	In atomoxetine trial 6962, the journal article cites zero SAEs in the 10-week acute phase [44]; three SAEs that were thought to be related to study medication (suicidal ideation, aggression, and self-injurious behavior) occurred in the 22-week extension phase reported in the trial summary.
	Not reporting SAEs that occurred during follow-up	In olanzapine trial 3045, the journal article stated "there were no deaths during the study," but failed to cite the death that occurred within 30 days after the study [45].
Difference in reporting criteria used	Not reporting SAEs that were presumed to be unrelated to the study drug	In these cases, journal articles would either make no mention at all of SAEs or would include a statement implying that SAEs did occur but without providing an exact figure, such as "No patients in either treatment group had a serious adverse event that was considered study medication related" [46]. In atomoxetine trial 5831, two SAEs thought to be "unlikely but possibly related" to the study drug were unreported in the associated journal article [47].
	Not reporting SAEs that were not statistically significantly different between treatment groups	In olanzapine trial 1032, 28 SAEs occurred in the randomized phase on which the journal article presents results. The journal article, however, contains no statement about SAE occurrence presumably because, as the trial summary indicates, there were no statistically significant differences in SAEs between treatment groups [48].
Apparent selective reporting of data	Omissions of SAE data	In sertraline trial 1060, the trial summary cites 5 SAEs in drug-treated participants, one of which occurred in the open-label phase and was thought by investigators to be related to the study drug. The journal article reports on the full length of the trial (open and double-blind phases), but only includes this statement related to SAEs: "No subjects had serious adverse events related to study treatment in either treatment group *during the double-blind phase*" [49] [emphasis added]. In olanzapine trial 2354, the journal article reports a lower number of SAEs than cited for the same study phase in the trial summary, and describes "the majority" of SAEs as "worsening of the illness" [50]. The trial summary reports a higher incidence of SAEs and more precisely details the events as suicidal ideation, suicide attempt, mania, and so on.

Figure 1. Clinical trial summary search results

Differences in Reporting Serious Adverse Events in Industry Sponsored Clinical Trial Registries and Journal Articles on Antidepressant and Antipsychotic Drugs - A Cross-sectional Study

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ABSTRACT

Objective: To examine the degree of concordance in reporting serious adverse events (SAEs) from ~~psychotropic~~ antidepressant and antipsychotic drug trials among journal articles and clinical trial summaries, and to categorize types of discrepancies.

Design: Cross-sectional study of summaries of all antidepressant and antipsychotic trials included in an online trial registry and their first associated stand-alone journal articles.

Setting: Clinicalstudyresults.org, sponsored by Pharmaceutical Research and Manufacturers of America; clinicaltrials.gov, administered by the US National Institutes of Health.

Main outcome measure: Three coders extracted data on the numbers and types of SAEs.

Results: 244 trial summaries for six antidepressant and antipsychotic drugs were retrieved, 142 (58.2%) listing an associated article. Of 1,608 SAEs in drug-treated participants according to trial summaries, 694 (43.2%) did not appear in associated articles. Nearly 60% of SAEs counted in articles and 41% in trial summaries had no description. Most cases of death (62.3%) and suicide (53.3%) were not reported in articles. Half or more of the 142 pairs were discordant in reporting the number (49.3%) or description (67.6%) of SAEs. These discrepancies resulted from journal articles' 1) omission of complete SAE data, 2) reporting acute phase study results only, and 3) more restrictive reporting criteria. Trial summaries with zero SAE were 2.35 (95% confidence interval, 1.58 to 3.49; P<0.001) times more likely to be published with no discrepancy in their associated journal article. Since clinicalstudyresults.org was removed from the Internet in 2011, only 7.8% of retrieved trial summaries appear with results on clinicaltrials.gov.

Conclusions: Substantial discrepancies exist in SAE data found in journal articles and registered summaries of antidepressant and antipsychotic drug trials. ~~The t~~Two main scientific sources accessible to clinicians and researchers are limited by incomplete, ambiguous, and inconsistent reporting. Access to complete and accurate data from clinical trials of drugs currently in use remains a pressing concern.

ARTICLE SUMMARY

Strengths and limitations of this study

- Published journal articles from antidepressant and antipsychotic drug trials report substantially fewer serious adverse events than associated clinical trial summaries posted by industry trial sponsors on a previously active online registry.
- Our findings of inconsistencies and ambiguities in serious adverse event reporting in both journal articles and trial summaries suggest that registries might not provide meaningfully improved access to complete and transparent clinical trial data.
- The registry from which we retrieved trial summaries has since been removed from the Internet and most trial summaries were not transferred with results to clinicaltrials.gov, making our analysis a unique examination of data that has been lost or scattered.
- We examined only the first stand-alone journal article associated with each trial summary, so it is possible that additional harms outcomes and longer-term outcomes absent from our sample of journal articles were reported in subsequent articles. Nevertheless, clear trends of incomplete reporting were apparent between journal article and trial summary sources.

INTRODUCTION

Publication bias and concerns regarding the integrity of the medical treatment knowledge base have led to various mechanisms, such as publicly accessible clinical trial registries, to promote transparent and complete reporting of clinical trial results [1, 2]. As the next most accessible source of drug information after published articles, clinical trial summaries available in online trial registries might contribute to improved evidence synthesis since they are supposed to provide an inclusive synopsis of both positive and negative results [3, 4]. In this study we compare serious adverse events (SAEs) found in industry-funded antipsychotic and antidepressant drug trial summaries posted by trial sponsors on an online trial registry, with SAEs found in published journal articles reporting on the same trials.

SAEs by definition result in death, hospitalization or significant disability and are therefore particularly important to report from a clinical trial because of their potential impacts on treatment decision-making and patient safety. International Conference on Harmonization (ICH) guidelines state that SAEs "deserve special attention" relative to other types of adverse effects, including providing individual-level patient detail and narrative for each SAE in clinical trial reports submitted to regulatory agencies [5]. Regulatory agencies in the United States and across Europe require trial sponsors to immediately report unexpected or life-threatening SAEs [6, 7]. However, the extent to which SAEs are then reported in outlets for clinicians, researchers, and the public is unknown, though evidence suggests incomplete and ambiguous reporting of harms-related data [8-10]. Recent settlements resulting from state and federal lawsuits in the United States against pharmaceutical manufacturers for minimizing or concealing drug harms, further highlight the need for increased diligence in discerning what important harm-related drug information might remain unknown or distorted in scientific outlets for reporting clinical trial

results [11-13]. While previous research has demonstrated that harms data are less completely reported in journal articles than clinical trial summaries, these studies provide primarily quantitative counts of reporting practices [8-10]. The present analysis seeks to elaborate the nature of quantitative and qualitative differences in SAE reporting, and possible explanations for reporting discrepancies.

Antipsychotic and antidepressant drugs — which rank among the 10 highest-selling drug classes in the U.S. and the world [14, 15] — are mainstay treatments in psychiatry and prescribed for myriad indicated and off-label, psychiatric and non-psychiatric uses [16, 17]. Journal publications, ~~and~~ clinical trial summaries posted on trial registries, and data from regulatory agencies such as the U.S. Food and Drug Administration (FDA) currently represent the primary information sources for clinicians and decision-makers regarding the safety and effectiveness of drug treatments. In contrast to substantially lengthier accounts of trials found in clinical study reports submitted to regulatory agencies, clinical trial summaries are abbreviated, concise descriptions of trials' background, methodology, and positive and negative results. ~~and, s~~Similar to clinical study reports, they are ~~prepared~~ structured according to templates described in the ICH *Guidelines for Industry: Structure and Content of Clinical Study Reports* [5], though their level of detail can vary substantially. Using the clinical trial summaries for all trials of these drugs posted by industry sponsors on clinicalstudyresults.org, we aimed to 1) count and describe SAEs reported in trial summaries and, as applicable, their associated peer-reviewed journal articles, 2) assess the consistency of SAE reporting between pairs of trial summaries and associated journal articles, and 3) categorize possible explanations for discrepant reporting.

METHODS

Data Sources

Clinical trials summaries were retrieved from clinicalstudyresults.org, the former online public registry sponsored by the Pharmaceutical Research and Manufacturers of America (PhRMA). Published journal articles were identified using the bibliography listed on the cover page of each trial summary.

2.1.1 Clinical trial summaries

The clinicalstudyresults.org registry was established in 2005 by PhRMA as a single repository for pharmaceutical manufacturers to post result summaries of their sponsored clinical trials. At the time, the federally funded clinicaltrials.gov, established in 2000 and administered by the U.S. National Institutes of Health, required manufacturers to register only the existence of their trials. According to PhRMA guidelines, complete results of all hypothesis-testing clinical trials completed after 2002 for products approved for marketing in the United States were to be submitted to its registry within one year after completion of the trial, and references to articles published in peer-reviewed journals added to the trial summary as soon as they were published [18].

In May 2011, we retrieved all Phase II, III, and IV clinical trial summaries (n=329) for all nine drugs within the antidepressant and antipsychotic classes listed on clinicalstudyresults.org. We excluded three drugs (desvenlafaxine, quetiapine, and venlafaxine) with registered trials but no or few posted trial summaries. For the remaining six drugs (n=254 trial summaries) we retained the summaries with trial completion dates on or before 2008, allowing at least 2.5 years for a trial to reach publication in the peer-reviewed literature (see Appendix Table 1). This resulted in 244 (74%) clinical trial summaries for six drugs from three manufacturers: aripiprazole (Abilify, Bristol-Myers Squibb), atomoxetine (Strattera, Eli Lilly), duloxetine (Cymbalta, Eli Lilly), olanzapine (Zyprexa, Eli Lilly), sertraline (Zoloft, Pfizer), and

ziprasidone (Geodon, Pfizer). Trial summaries averaged 18 pages in length (range: 3 to 147). Supplementary File 1 provides a trial summary illustrating the typical format of the documents in this sample. Trial summaries include both pre-marketing studies that were sent to regulatory agencies for drug approval and post-marketing studies for new indications, additional outcomes, and long-term follow-up.

Journal articles

~~Using~~ We used the bibliography listed on the cover page of each trial summary~~, we counted a total of 496 listed publications (an average of two publications per trial, with an average time to publication of 2.5 years), from which we~~ to retrieve~~d~~ the earliest journal article reporting on the full trial. From the total we excluded 261 (52.6%) sub-set analyses (i.e., reports on a sub-set of the total sample based on a shared characteristic, such as gender), meta-analyses, and conference abstracts. Of the 244 trial summaries, 142 (58.2%) listed an associated stand-alone journal article.~~ We emailed and telephoned the medical communications, clinical trials, or customer relations department of each manufacturer of the included drugs to inquire about the completeness of the list of trial summaries and journal articles posted on clinicalstudyresults.org. No representative from any manufacturer could confirm completeness of the posted lists nor provide a current list of all clinical trials and journal publications for the respective drugs. Representatives directed us to visit clinicaltrials.gov to view current and completed trials, and PubMed for a list of publications. We then attempted to manually search PubMed to match possible additional publications with the trial summaries, but the absence of trial identification numbers in journal articles made it extremely difficult to crosscheck and match all sources reliably. ~~-~~These additional efforts, therefore, did not affect the final sample size~~,~~ ~~which consisted~~

~~of 142 trial summary-journal article pairs listed on clinicalstudyresults.org and an additional 102 trial summaries from the registry with no associated journal article (see Figure 1).~~

Data Extraction

We employed double data extraction. One coder extracted the number and exact description of SAEs reported to occur in drug-treated participants from the *Results* section of each ~~of the 244~~ trial summar~~yies~~ and ~~142~~ journal article~~s~~. For multi-phase trials, we tallied the SAEs occurring in each phase. The number of patients experiencing SAEs was counted in the few cases where the number of events was not provided, therefore underestimating the actual number of SAEs. We also extracted from each source the trial start and completion year, article publication date, study length, sample size, targeted indication, and consistency of reporting SAEs (see explanation below). A second coder independently extracted these data from a 50% random sample of trial summaries and articles for three of the six drugs. A third coder repeated the same process for the other three drugs. The values obtained by the second and third coders were compared to those obtained by the first. Any discrepancies were resolved by consensus. Coding for most reports and articles was straightforward and few disagreements in recordings between coders were found.

We evaluated the consistency of the number and description of SAEs occurring in drug-treated participants reported between each trial summary and its associated article ~~(142 pairs)~~. The *number* of SAEs was considered inconsistent if (1) reported numbers differed between the two sources (e.g., aripiprazole trial CN138-008: trial summary cited 7, journal article 6, SAEs), (2) one source reported the number of SAEs while the other contained no or an ambiguous statement about their occurrence; or (3) the journal article did not report the trial phase in which SAEs did occur according to the trial summary (e.g., ziprasidone trial 1006: in a 60-week multi-

phase study with 8 SAEs reported in the summary, the article reports findings from the 8-week acute phase with zero SAEs). The *description* of SAEs was considered inconsistent if only one source described the events (e.g., duloxetine trial 6091: the summary describes 1 SAE as an intentional overdose, the article omits the description but accurately reports the number), or if one source less completely described the events than the other source (e.g., duloxetine trial 8601: the summary lists one death from suicide as well as other SAEs related to psychiatric worsening, but the article mentions only the suicide). Sources were considered consistent if both reported the number or description of SAEs identically, or if neither reported such information. In each instance of discrepant reporting, we performed an in-depth inductive analysis involving a carefully reviewed review of the trial summary and journal article to clarify identify a possible explanation for the form of the inconsistency discrepancy. We then grouped the emerging patterns, which resulted in three categories (described in the results section): differences in study length or phase reported, differences in reporting criteria used, and apparent selective reporting of SAE data. and then categorized our findings. Discrepancies were only assigned to the latter category after ruling out the other two explanations. No additional categories to explain discrepant reporting emerged from the analysis.

Analysis

We used descriptive statistics to summarize quantitative variables related to study characteristics and frequencies for categorical variables. We calculated the number of SAEs per patient treated for each drug by dividing the number of SAEs reported in trial summaries and journal articles, respectively, by the total number of drug-treated participants.

We extracted exact descriptions of SAEs and then categorized them as: behavioral or cognitive, physical, no description provided, and unspecified (including overdose, dependence,

death or hospitalization for unspecified reasons, and accidental injury). We further counted the number of SAEs reported as death, suicide, suicide attempt, homicidal ideation, and new or worsened psychiatric symptoms.

We calculated risk ratios to test the likelihood of trial summaries reporting zero SAEs to be published as stand-alone journal articles in a manner congruent with the summaries, compared to trial summaries reporting ≥ 1 SAEs. Risk ratios were calculated with 95% confidence intervals and Pearson's chi-square analysis using PASW Statistics, version 18 software [19].

RESULTS

Search Results and Sample Selection

Using the bibliography listed on the cover page of each trial summary, we counted a total of 496 listed publications (an average of two publications per trial, with an average time to publication of 2.5 years), from which we retrieved the earliest journal article reporting on the full trial. From the total we excluded 261 (52.6%) sub-set analyses (i.e., reports on a sub-set of the total sample based on a shared characteristic, such as gender), meta-analyses, and conference abstracts. Of the 244 trial summaries, 72 (29.5%) listed no publication of any kind, 30 (12.3%) listed only one or more of the excluded publication types, and 142 (58.2%) listed at least one associated stand-alone journal article (see Figure 1). The final sample consisted of 142 trial summary-journal article pairs listed on clinicalstudyresults.org and an additional 102 trial summaries from the registry with no associated journal article.

Sample Description

For each of the six drugs included in this analysis, Table 1 summarizes trial characteristics as reported in trial summaries, their associated journal articles, and the additional trial summaries having no associated journal article (referred to as *unpublished trial summary* on

all tables and appendices). Overall, a stand-alone journal article was available for 58.2% of trials in this sample, though this varied by drug from a low of 27.6% for trials of ziprasidone to 72.9% for trials of duloxetine. Journal articles reported findings for an identical or nearly identical number of participants as their associated trial summaries. The 102 unpublished summaries, however, included data on an additional 20,084 drug-treated participants. The median study length was shorter in journal articles (11 weeks) than in their paired trial summaries (12 weeks) or unpublished trial summaries (16 weeks).

The three antipsychotic drugs (n=129 trial summaries) were being tested for the treatment of psychotic disorders (56.6% of studies), bipolar disorder or mania (26.4%), or other conditions (16.2%) such as depressive disorders, Alzheimer's, autism, alcohol dependence, or borderline personality disorder. The three antidepressant drugs (n=115 trial summaries) were being studied for the treatment of attention deficit hyperactivity disorder (42.6%), depressive disorders (34.8%), anxiety disorders (8.7%), or other conditions (14%) such as pain-related disorders or post-traumatic stress disorder.

Serious Adverse Events in Trial Summaries

Ninety percent of all trial summaries (n=244) reported a precise number of SAEs occurring in the trial. The 142 trial summaries with an associated journal article reported 1,608 SAEs, and the 102 trial summaries with no associated journal article reported an additional 1,423 SAEs. Table 2 details the total and per patient numbers of SAEs reported in trial summaries for each drug. Appendix Table 2 lists additional SAEs for the 10 excluded trial summaries with trial completion dates in 2009 or later.

No description was provided for 41% of the SAEs cited in trial summaries (46% and 20% of SAEs in antipsychotic and antidepressant trials, respectively). An additional 11.6% of SAEs

were non-specifically described, such as "accidental injury" in duloxetine trial 1126. When a specific description was present, we categorized 28.4% of SAEs as behavioral or cognitive and 18.9% as physical. Table 3 details all cases of death, suicide, and new or worsened psychiatric symptoms for each drug.

Serious Adverse Events in Journal Articles

Nearly 40% of journal articles failed to specify the number of SAEs that occurred in the trial (Table 2), containing either no statement related to SAEs or an ambiguous statement without an actual number of SAEs, such as sertraline trial 1060: "no subjects had serious adverse events related to study treatment." A total of 914 SAEs were reported across the 85 journal articles that did include specific data on SAE occurrence.

Most SAEs (58.9%) reported in journal articles (61% in antipsychotic and 55.5% in antidepressant trials) had no accompanying description and another 8% were non-specifically described. Nearly one-fifth (18.9%) of SAEs were behavioral or cognitive in nature and 14.6% were described as physical. Table 3 shows that one-quarter of SAEs described in journal articles were categorized as death, suicide, homicidal ideation, or new or worsened psychiatric symptoms.

Consistency of Reporting in Trial Summary-Journal Article Pairs

Just over half (56.8%) of the 1,608 SAEs experienced by drug-treated participants according to trial summaries (n=142) were also reported in associated journal articles. This proportion varied widely between the drugs, from 14.8% of SAEs in atomoxetine trials to 114.6% in aripiprazole trials (see Table 2). The number of SAEs per patient for most drugs were lower in articles (0.03, range: 0.003 - 0.07) than in associated summaries (0.05, range: 0.02 –

0.13). Trial summaries with no associated article averaged the highest number of SAEs per patient (0.07, range: 0.01 – 0.14).

Half or more of the 142 trial summary-journal article pairs were discordant in reporting the number (49.3%) or description (67.6%) of SAEs (Table 4). In half of these pairs, the reported number of SAEs differed by more than 20% between the two sources.

Both journal articles and associated trial summaries failed to describe a substantial proportion of SAEs. Most cases of death (62.3%) and suicide (53.3%) cited in trial summaries were not reported in associated journal articles (Table 3).

The 34 trial summaries with zero SAEs were 2.35 (95% confidence interval, 1.58 to 3.49; P<0.001) times as likely to have an associated journal article reporting this data consistently with the trial summary data as were the 181 summaries with 1 or more SAEs.

Explanations for Discrepant Reporting

Seventy (49.3%) of the 142 trial summary-journal article pairs were discrepant in SAE reporting. ~~Nearly h~~Half of these instances might be explained by differences between sources in the study length or phase being reported (25%, 18/70) or in the reporting criteria used (~~24.3~~25%, 18/70). Table 5 provides examples of each of these forms of discrepant reporting. Importantly, while some journal articles appeared to apply more restrictive reporting criteria that might lead to omitting certain data, the many articles that did report exact SAE numbers often did so regardless of presumed causality to the study drug. For example, articles and summaries for olanzapine trials 3131 and 7031 reported all SAEs even though some events were thought to be unrelated to the study drug. Yet, the article for olanzapine trial 4414 separately details SAEs thought to be related and unrelated to the drug [20]. Thus, no clear or consistent pattern on SAE reporting criteria emerged from this sample of journal articles.

Another one-third (~~32.9~~34.3%, 24/70) of discrepancies appear to be simple failures of journal articles to report complete SAE data (see Table 5). In a minority (~~13~~14.3%, 10/70) of cases, however, the journal article provided more precise data or a higher number of SAEs than the trial summary. The article for aripiprazole trial CN138-050, for example, cites 6 SAEs in drug-treated participants [21], while the summary states only that the incidence of SAEs was low.

Post Hoc Analysis of Clinical Trial Summaries on Clinicaltrials.gov ~~y Availability~~

In December 2011, clinicalstudyresults.org was removed from the Internet for unknown reasons. The Internet archive for the website (found here: Internet archive) suggests that the expansion of other registries made clinicalstudyresults.org seem redundant from industry's perspective [22]. One year after this removal of the registry, we cross-checked our data source by searching for each of the 244 trial summaries on clinicaltrials.gov. (In that database, the U.S. Food and Drug Administration Amendment Act [FDAAA] of 2007 newly mandated trial sponsors to include summary reporting of results for trials that were initiated after or ongoing as of late 2007.) Our search revealed that 139 (57%, range across drugs: 25% - 80%) of the 244 trials were registered on clinicaltrials.gov, but only 15 of these (10.8%, range across drugs: 0% - 39%) had posted study results. In October 2013, nearly two years after the clinicalstudyresults.org takedown, these numbers had only slightly budged, with 19 registered trials now reporting study results. While nearly all (99%) of the trial summaries not currently registered on clinicaltrials.gov have trial start or completion dates prior to 2007, 75% of trial summaries that *are* registered on the website also have pre-2007 trial dates. In the interest of openness and transparency, we created a publicly accessible website (www.rxarchives.com) where all 244 trial summaries are posted in pdf format and freely available for download. ~~*fNote*~~

~~*to reviewers: the website, rxarchives.com, will become live at the time of this manuscript's publication]*~~

DISCUSSION

This study demonstrates that a substantially lower number of SAEs appear in published journal articles than registered trial summaries of antidepressant and antipsychotic drug trials, and shows further that both sources for drug information are often inconsistent or ambiguous in SAE reporting. In this study, 43.2% of all SAEs appearing in 142 trial summaries posted on an online registry across six psychotropic drugs were not reported in the first associated stand-alone journal articles listed by the drug's manufacturer. Failure to describe the nature of SAEs was also common in both sources. Given that many consumers of psychotropic drugs take these medications for months or years, that approximately one-quarter of journal articles reported only acute phase results of longer-term trials and that the median study length in trial summaries with an associated journal article (12 weeks) was four weeks shorter than in trials without a journal article highlight an additional attrition of evidence on longer term outcomes.

These findings are congruent with other recent analyses demonstrating more complete outcomes information in registered clinical trial summaries compared to published journal articles [9], although examination of full clinical study reports reveals that both of the latter sources suffer from incomplete reporting of key data [10]. Similar to our results, Riveros and colleagues [9] found that registered trial summaries (99%; present study 90%) more often report data on serious adverse events compared to published articles (63%; present study 60%). However, in an analysis comparing publicly available data in registered clinical trial summaries and journal publications to full clinical study reports submitted to a regulatory agency for drug products, the former sources reported complete information on harms outcomes significantly less

(~25%) than clinical study reports (87% of harms outcomes reported completely) [10]. SAEs, specifically, were reported completely only 51% of the time in journal articles and trial summaries, and 30% of SAE outcomes were not reported at all in these sources. In their analysis of full clinical study reports on the influenza drug Tamiflu, Doshi, Jefferson, and Del Mar [3] are alarmed by the important data remaining unknown to most physicians when clinical trial information is limited to the published journal literature. The occurrence of SAEs and the rationales for classifying events as adverse are among many possible discoveries in clinical study reports that can markedly alter a drug's benefit-to-risk profile. While publication bias of this sort in the literature has long been acknowledged or suspected [23-25], the present study clarifies the degree to which such bias distorts the perception of important harms outcomes (i.e., number and nature of SAEs) across two classes of popularly used psychotropic drugs. Also, this study adds to the evidence base questioning whether information posted in online clinical trial registries represents meaningful improvement.

For another 102 trials with no associated stand-alone journal article in the present study, the clinical trial summaries report an additional 1,423 SAEs and represent the only publicly available data source on these trials. In a recent examination of 585 large randomized trials registered on clinicaltrials.gov, 29% had no associated journal publication and most (78%) of those also had no results available on the clinicaltrials.gov registry [26]. Riveros and colleagues [9] found that 50% of 594 randomly sampled controlled drug trials on clinicaltrials.gov had no corresponding published article. These findings highlight the necessity for clinicians, researchers, and decision-makers to consult multiple sources in order to achieve a comprehensive and more complete appraisal of drugs' safety profile, although again, clinical trial summaries are

themselves limited by incomplete reporting [10, 27] and by regulatory policies that require registration of only recent [1] or new trials [28].

Our post hoc analysis further revealed that, while 57% (139/244) of the present sample of trial summaries are registered on clinicaltrials.gov, only 7.8% (19/244) are available on the registry with results. Three-quarters of these currently registered trials have trial start or completion dates prior to 2007, thereby suggesting that actual registration practices on clinicaltrials.gov may be more inclusive than the minimum requirements set out by the FDAAA. Access to the full evidence base of drugs currently in use, including recent studies and those conducted prior to widespread deployment of registries, is essential for sound treatment decision-making and the assurance of present day patient safety [10, 29], but the important efficacy and harms information contained in these 225 trials on six psychotropic drugs has been lost or scattered. As of this writing, Pfizer (sertraline and ziprasidone) and Bristol-Myers Squibb (aripiprazole) company websites include trial summaries or links to clinicaltrials.gov only for trials completed or ongoing as of 2007, in accordance with FDAAA guidelines. All clinical trial summaries included in the present analysis for atomoxetine, duloxetine, and olanzapine are available on Eli Lilly's company website. Some data, then, have been lost to the evidence base with the removal of clinicalstudyresults.org, while other data are still available but no longer accessible through a single repository. The important harms data contained in the present body of trial summaries provides further support for the recommendation that all ongoing, recent, and archive drug trials for all new and existing drugs be made available to clinicians and consumers in a clear and accessible format, including links between all trial-related documents (journal articles, registry records, trial protocol, and so on) for transparent navigation of each trial component to the core study [10, 30, 31].

The present study has important limitations and strengths. First, although participating industry trial sponsors had posted on their respective websites statements of their commitment to posting all trial results in a timely manner on clinicalstudyresults.org, the completeness and accuracy of trial summaries on clinicalstudyresults.org could not be verified. However, since our crosscheck of summaries on clinicaltrials.gov revealed that few of these trials were transferred with results, our present analysis provides a glimpse on unique trial evidence that a contemporary standard database fails to capture. Second, only the first stand-alone journal article for each trial was included in this analysis. For trials with multiple publications, additional information on SAEs might appear in subsequent articles. However, this possibility might be slight as the median number of journal articles per trial summary was one, and over half of total articles listed for the six drugs were pooled or sub-set analyses or conference abstracts. We do not know whether the trends observed in the 142 trial summary-journal article pairs would hold for the other 102 trials. Finally, the results of this study cannot be generalized to other drugs and drug classes, but do add to the substantial body of empirical findings demonstrating poor adverse event assessment and reporting practices and a distortion of evidence through selective reporting of industry-sponsored psychotropic drug research [24, 32-35].

The integrity of the medical treatment knowledge base preserves sound clinical practice and ensures patient safety. If nearly half of serious adverse events in psychotropic drug research are not reported in journal articles and many more can be found in sources not easily accessed by relevant treatment decision-makers [3, 10, 36], then, without integrating multiple data sources, benefit-to-harm assessments made by groups constructing clinical guidelines and by individual clinicians making prescription decisions are based on incomplete evidence and likely biased toward underestimating risks. Multiple solutions to the grave problem of incomplete reporting of

clinical trials have been proposed, and some recent strides have been made. Some suggest shifting toward public funding and control of drug research in order to produce credible information accessible and transparent to all stakeholders [37-40]. Some propose to treat failures to disclose complete knowledge of adverse effects from clinical trials as criminal offenses requiring criminal prosecution of responsible individuals and companies [41]. At the same time, ongoing campaigns have gained momentum across the United Kingdom in calling for pharmaceutical manufacturers to share clinical study reports on all drugs in use [31] and in the United States for sharing clinical trial datasets with independent scientists [42]. Many agree, however, that regulatory requirements for registering new and ongoing studies does not adequately protect the millions of patients currently taking prescription drugs [10, 31], and the pharmaceutical industry has been slow and resistant to accepting the level of openness that scientists and the public have been calling for [31, 43].

The present findings highlight inconsistencies in harms-related reporting between published articles and trial registry summaries of psychotropic drugs, and indicate that clinical decisions regarding drug use may be based on substantially truncated evidence. Policy discussions in this area should consider to what extent patients who use drugs, clinicians who prescribe drugs and the public who finance most of their use deserve access to complete and accurate scientific data from drug trials.

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Data Sharing: All clinical trial summaries that were analysed in this study have been uploaded by the first author (S.H.) to a publicly-accessible website (www.rxarchives.com) for download.

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Figure 1. Clinical trial summary search results

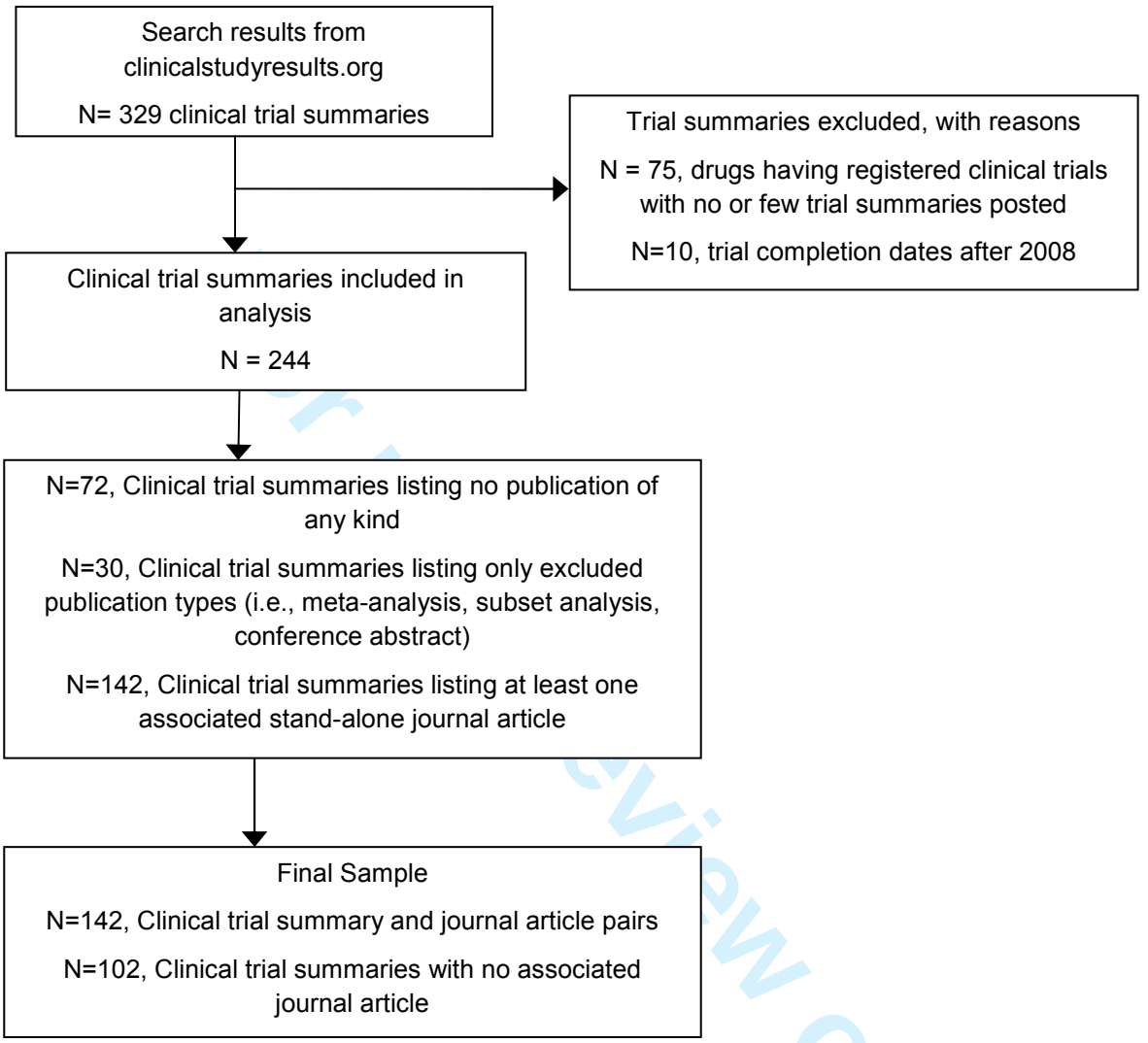


Table 1. Description of included studies

	N	Modal trial completion or article publication year	Average (median) number of publications per trial[a]	Average years from trial completion to article publication	Average (median) trial length in weeks	Maximum trial length in weeks	Number of drug treated participants (% as reported in summaries)	Total no. participants
Aripiprazole								
Trial summary	28	2006	0.62 (1)	2.6	20.8 (8)	140	5,809	9,935
Journal article	28	2009	--	--	10.7 (8)	52	5,696 (98)	9,728
Unpublished trial summary[b]	21	2003	--	--	29.9 (26)	94	6,896	8,112
Olanzapine								
Trial summary	33	2000	1.78 (1)	2.7	26.5 (24)	78	8,515	12,136
Journal article	33	2002	--	--	16.8 (6)	78	8,225 (97)	11,932
Unpublished trial summary	18	2005	--	--	18.7 (19)	48	3,120	4,997
Ziprasidone								
Trial summary	8	2005	0.79 (0)	3.8	17.1 (12)	60	910	1,399
Journal article	8	2007	--	--	10.5 (10)	27	910 (100)	1,399
Unpublished trial summary	21	2008	--	--	38.4 (12)	320	3,268	4,459
Atomoxetine								
Trial summary	31	2005	1.76 (1)	2.2	35.9 (18)	181	4,313	7,094
Journal article	31	2007	--	--	16.7 (10)	97	4,138 (96)	6,975
Unpublished trial summary	20	2006	--	--	35.7 (24)	104	3,640	4,469
Duloxetine								
Trial summary	35	2005	4.69 (3)	2	27.1 (13)	103	14,185	18,334
Journal article	35	2007	--	--	22.8 (13)	103	14,185 (100)	18,334
Unpublished trial summary	13	2004	--	--	24.2 (15)	62	2,115	3,413
Sertraline								
Trial summary	7	2003	1.53 (1)	2.9	37.7 (22)	128	2,147	2,326
Journal article	7	2005	--	--	22.9 (22)	52	2,147 (100)	2,326
Unpublished trial summary	9	2001	--	--	15.4 (10)	36	1,045	1,541
All Drugs								
Trial summary	142	2005	2 (1)	2.5	27.8 (12)	181	35,879	51,224
Journal article	142	2007	--	--	16.7 (11)	103	35,269 (98)	50,694
Unpublished trial summary	102	2006	--	--	28.8 (16)	320	20,084	26,992

[a]Average and median number of publications reflect all publications listed on the trial summary cover page, including stand-alone journal articles, meta-analyses, sub-set analyses, and conference abstracts.
[b]Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

Table 2. Number of serious adverse events (SAEs) reported in trial summaries and journal articles for drug-treated participants

	Number (%) of studies that report the number of SAEs[a]	Number of SAEs (% as reported in associated trial summaries)	Number of SAEs per patient treated[b]
Aripiprazole			
Trial summary (n=28)	26 (92.9)	364	0.06
Journal article (n=28)	27 (96.4)	417 (114.6%)	0.07
Unpublished trial summary[c] (n=21)	20 (95.2)	504	0.07
Olanzapine			
Trial summary (n=33)	28 (84.8)	544	0.06
Journal article (n=33)	11 (33.3)	66 (12.1%)	0.008
Unpublished trial summary (n=18)	17 (94.4)	302	0.10
Ziprasidone			
Trial summary (n=8)	7 (87.5)	117	0.13
Journal article (n=8)	5 (62.5)	53 (45.3%)	0.06
Unpublished trial summary (n=21)	21 (100.0)	446	0.14
Atomoxetine			
Trial summary (n=31)	25 (80.6)	88	0.02
Journal article (n=31)	14 (45.2)	13 (14.8%)	0.003
Unpublished trial summary (n=20)	17 (85.0)	35	0.01
Duloxetine			
Trial summary (n=35)	32 (91.4)	453	0.03
Journal article (n=35)	27 (77.1)	349 (77%)	0.02
Unpublished trial summary (n=13)	12 (92.3)	117	0.06
Sertraline			
Trial summary (n=7)	7 (100.0)	42	0.02
Journal article (n=7)	2 (28.6)	16 (38.1%)	0.007
Unpublished trial summary (n=9)	8 (88.9)	19	0.02
All Drugs			
Trial summary (n=142)	125 (88.0)	1,608	0.05
Journal article (n=142)	85 (59.9)	914 (56.8%)	0.03
Unpublished trial summary (n=102)	95 (93.1)	1,423	0.07

[a]The figures in this column indicate those publications that reported the number of SAEs that occurred. Some publications contained no statement about the occurrence of SAEs or contained an ambiguous statement without specifying the actual number of SAEs, such as "No SAEs thought to be related to study medication occurred."
[b]The numerator equals the number of events; the denominator equals the total number of drug-treated participants, as reported in Table 1.
[c]Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

Table 3. Number of deaths, suicide- and homicide-related events, and psychiatric serious adverse events in drug-treated participants

	Death	Suicide, completed	Suicidal ideation, attempts, injury	Homicidal ideation	New or worsened psychiatric symptoms	Total
Aripiprazole						
Trial summary (n=28)	79	1	4	0	79	163
Journal article (n=28)	27 (34.2)[a]	1 (100.0)	5 (125.0)	0	66 (83.5)	99 (60.7)
Unpublished trial summary[b] (n=21)	15	1	10	0	92	118
Olanzapine						
Trial summary (n=33)	50	9	18	0	85	162
Journal article (n=33)	19 (38.0)	1 (11.1)	4 (22.2)	0	14 (16.5)	38 (23.5)
Unpublished trial summary (n=18)	7	3	21	1	95	127
Ziprasidone						
Trial summary (n=8)	0	1	13	1	30	45
Journal article (n=8)	0 (0)	1 (100.0)	5 (38.5)	1 (100.0)	14 (46.7)	20 (44.4)
Unpublished trial summary (n=21)	18	1	23	3	141	186
Atomoxetine						
Trial summary (n=31)	0	0	7	0	6	13
Journal article (n=31)	0	0	0 (0)	0	0 (0)	0 (0)
Unpublished trial summary (n=20)	1	0	5	0	5	11
Duloxetine						
Trial summary (n=35)	11	4	40	0	27	82
Journal article (n=35)	11 (100.0)	4 (100.0)	33 (82.5)	0	21 (77.8)	69 (84.1)
Unpublished trial summary (n=13)	3	0	10	0	20	33
Sertraline						
Trial summary (n=7)	11	0	5	0	11	27
Journal article (n=7)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)
Unpublished trial summary (n=9)	1	0	10	1	4	16
All Drugs						
Trial summary (n=142)	151	15	87	1	238	492
Journal article (n=142)	57 (37.7)	7 (46.7)	47 (54.0)	1 (100.0)	115 (48.3)	227 (46.1)
Unpublished trial summary (n=102)	45	5	79	5	357	491

[a]Percent as reported in associated trial summaries.
[b]Unpublished trial summary refers to clinical trial summaries posted on the publicly accessible clinicalstudyresults.org website, but having no associated stand-alone journal article.

Table 4. Percentage of trial summary -journal article pairs that report serious adverse event (SAE) data consistently across sources

Summary-Article Pairs	Number of SAEs		Description of SAEs
	Consistent across sources	> 20% difference across sources	Consistent across sources
Aripiprazole (n=28)	67.9	25.0	28.6
Olanzapine (n=33)	27.3	72.7	30.3
Ziprasidone (n=8)	37.5	37.5	37.5
Atomoxetine (n=31)	54.8	45.2	42.0
Duloxetine (n=35)	62.9	37.1	31.4
Sertraline (n=7)	28.6	71.4	14.3
All Drugs (n=142)	50.7	49.2	32.4

Table 5. Explanations for Discrepant Reporting of SAEs between Journal Articles and Trial Summaries

~~Category~~ General explanation for discrepant reporting	Specific explanation for discrepant reporting	Example
Difference in study length or phase reported	Reporting only one phase of a multi-phase trial	In atomoxetine trial 6962, the journal article cites zero SAEs in the 10-week acute phase [44]; three SAEs that were thought to be related to study medication (suicidal ideation, aggression, and self-injurious behavior) occurred in the 22-week extension phase reported in the trial summary.
	Not reporting SAEs that occurred during follow-up	In olanzapine trial 3045, the journal article stated "there were no deaths during the study," but failed to cite the death that occurred within 30 days after the study [45].
Difference in reporting criteria used	Not reporting SAEs that were presumed to be unrelated to the study drug	In these cases, journal articles would either make no mention at all of SAEs or would include a statement implying that SAEs did occur but without providing an exact figure, such as "No patients in either treatment group had a serious adverse event that was considered study medication related" [46]. In atomoxetine trial 5831, two SAEs thought to be "unlikely but possibly related" to the study drug were unreported in the associated journal article [47].
	Not reporting SAEs that were not statistically significantly different between treatment groups	In olanzapine trial 1032, 28 SAEs occurred in the randomized phase on which the journal article presents results. The journal article, however, contains no statement about SAE occurrence presumably because, as the trial summary indicates, there were no statistically significant differences in SAEs between treatment groups [48].
Apparent selective reporting of data	Omissions of SAE data	In sertraline trial 1060, the trial summary cites 5 SAEs in drug-treated participants, one of which occurred in the open-label phase and was thought by investigators to be related to the study drug. The journal article reports on the full length of the trial (open and double-blind phases), but only includes this statement related to SAEs: "No subjects had serious adverse events related to study treatment in either treatment group *during the double-blind phase*" [49] [emphasis added].

	In olanzapine trial 2354, the journal article reports a lower number of SAEs than cited for the same study phase in the trial summary, and describes "the majority" of SAEs as "worsening of the illness" [50]. The trial summary reports a higher incidence of SAEs and more precisely details the events as suicidal ideation, suicide attempt, mania, and so on.

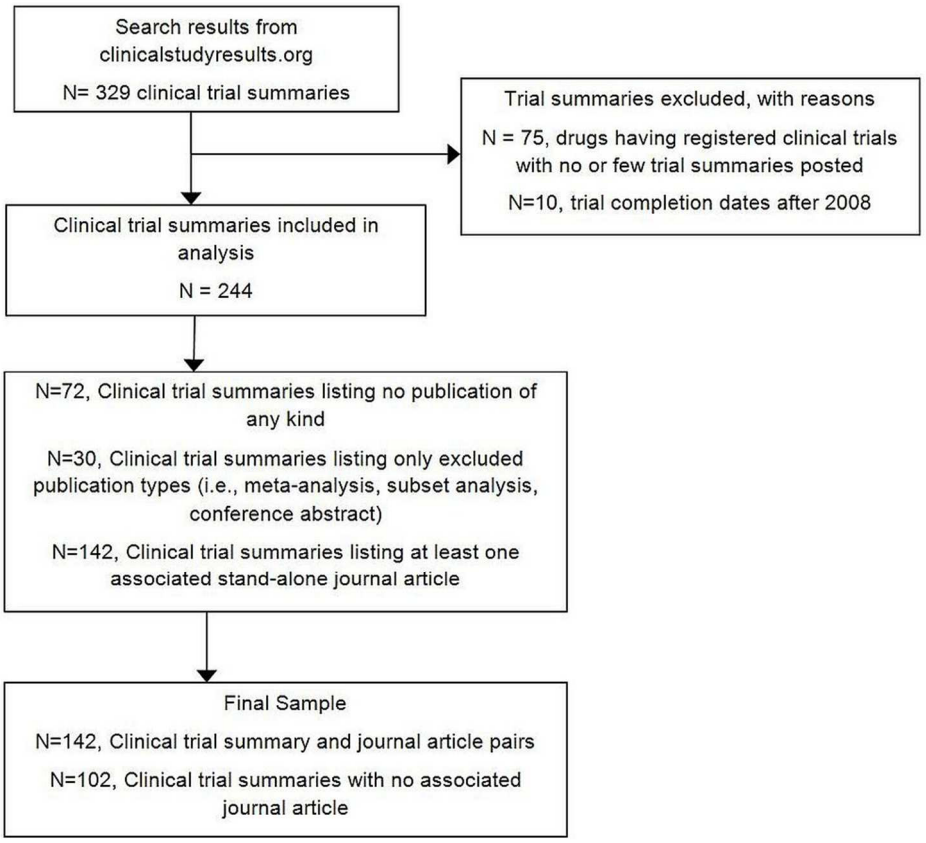
Appendix Table 1. Trial completion dates and time to journal article publication for six psychotropic drugs on clinicalstudyresults.org

	1999 or earlier	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009 or later
Aripiprazole											
Number of completed trials	0	0	3	5	10	5	4	11	8	3	3
(% published as stand-alone article)[a]			(66.7)	(40)	(40)	(100)	(75)	(54.5)	(37.5)	(100)	(0)
Average years to article publication	--	--	3	5	5	2.4	3	2	1.7	1	n/a
Olanzapine											
Number of completed trials	12	7	2	7	3	0	7	8	4	1	0
(% published as stand-alone article)	(91.7)	(100)	(100)	(85.7)	(33.3)		(28.6)	(37.5)	(0)	(100)	
Average years to article publication	2.2	2.3	4	3.5	3	--	3	3	n/a	1	--
Ziprasidone											
Number of completed trials	0	0	0	2	5	4	7	2	1	8	5
(% published as stand-alone article)				(50)	(20)	(25)	(42.9)	(100)	(0)	(0)	(0)
Average years to article publication	--	--	--	5	2	6	3.7	3	n/a	n/a	n/a
Atomoxetine											
Number of completed trials	1	2	6	6	6	7	8	12	3	0	0
(% published as stand-alone article)	(100)	(100)	(66.7)	(83.3)	(66.7)	(71.4)	(75)	(16.7)	(66.7)		
Average years to article publication	3	2	2.3	2.6	2.8	2.8	1.8	1	1	--	--
Duloxetine											
Number of completed trials	3	1	6	4	5	7	10	4	8	0	1
(% published as stand-alone article)	(0)	(100)	(66.7)	(100)	(100)	(57.1)	(90)	(75)	(62.5)		(0)
Average years to article publication	n/a	2	1.8	3	2.8	2	2.1	1.3	1.4	--	n/a
Sertraline											
Number of completed trials	4	0	3	0	5	0	2	0	2	0	0
(% published as stand-alone article)	(75)		(0)		(80)		(0)		(0)		
Average years to article publication	4.3	--	n/a/	--	1.8	--	n/a	--	n/a	--	--
All Drugs											
Number of completed trials	20	10	20	24	34	23	38	37	26	12	10
(% published as stand-alone article)	(75)	(100)	(60)	(75)	(56)	(65)	(60)	(43)	(38)	(33)	(0)
Average years to article publication	3.2	2.1	2.8	3.8	2.9	3.3	2.7	2.1	1.4	1	n/a

[a] Meta-analyses and sub-set analyses published in journals and conference abstracts are not included in the percent published.

Appendix Table 2: Drug-treated participants and serious adverse events (SAEs) among ten trial summaries of clinical trials completed in 2009 or later (excluded from the published analysis)

	Number of excluded trial summaries	Number of drug- treated participants	Total number of SAEs in drug-treated participants	Number of SAEs			
				Death	Suicide, completed	Suicidal ideation, attempt, injury	New or worsened psychiatric symptoms
Aripiprazole	3	676	39	1	1	1	2
Olanzapine	0	NA	NA	NA	NA	NA	NA
Ziprasidone	5	1436	124	3	2	9	57
Atomoxetine	0	NA	NA	NA	NA	NA	NA
Duloxetine	1	657	2	0	0	0	1
Sertraline	1	157	2	0	0	1	0
All Drugs	10	2926	167	4	3	11	60



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Appendix Table 1. Trial completion dates and time to journal article publication for six psychotropic drugs on clinicalstudyresults.org

	1999 or earlier	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009 or later
Aripiprazole											
Number of completed trials	0	0	3	5	10	5	4	11	8	3	3
(% published as stand-alone article)[a]			(66.7)	(40)	(40)	(100)	(75)	(54.5)	(37.5)	(100)	(0)
Average years to article publication	--	--	3	5	5	2.4	3	2	1.7	1	n/a
Olanzapine											
Number of completed trials	12	7	2	7	3	0	7	8	4	1	0
(% published as stand-alone article)	(91.7)	(100)	(100)	(85.7)	(33.3)		(28.6)	(37.5)	(0)	(100)	
Average years to article publication	2.2	2.3	4	3.5	3	--	3	3	n/a	1	--
Ziprasidone											
Number of completed trials	0	0	0	2	5	4	7	2	1	8	5
(% published as stand-alone article)				(50)	(20)	(25)	(42.9)	(100)	(0)	(0)	(0)
Average years to article publication	--	--	--	5	2	6	3.7	3	n/a	n/a	n/a
Atomoxetine											
Number of completed trials	1	2	6	6	6	7	8	12	3	0	0
(% published as stand-alone article)	(100)	(100)	(66.7)	(83.3)	(66.7)	(71.4)	(75)	(16.7)	(66.7)		
Average years to article publication	3	2	2.3	2.6	2.8	2.8	1.8	1	1	--	--
Duloxetine											
Number of completed trials	3	1	6	4	5	7	10	4	8	0	1
(% published as stand-alone article)	(0)	(100)	(66.7)	(100)	(100)	(57.1)	(90)	(75)	(62.5)		(0)
Average years to article publication	n/a	2	1.8	3	2.8	2	2.1	1.3	1.4	--	n/a
Sertraline											
Number of completed trials	4	0	3	0	5	0	2	0	2	0	0
(% published as stand-alone article)	(75)		(0)		(80)		(0)		(0)		
Average years to article publication	4.3	--	n/a/	--	1.8	--	n/a	--	n/a	--	--
All Drugs											
Number of completed trials	20	10	20	24	34	23	38	37	26	12	10
(% published as stand-alone article)	(75)	(100)	(60)	(75)	(56)	(65)	(60)	(43)	(38)	(33)	(0)

Average years to article publication	3.2	2.1	2.8	3.8	2.9	3.3	2.7	2.1	1.4	1	n/a

[a] Meta-analyses and sub-set analyses published in journals and conference abstracts are not included in the percent published.

Appendix Table 2: Drug-treated participants and serious adverse events (SAEs) among ten trial summaries of clinical trials completed in 2009 or later (excluded from the published analysis)

	Number of excluded trial summaries	Number of drug- treated participants	Total number of SAEs in drug-treated participants	Number of SAEs			
				Death	Suicide, completed	Suicidal ideation, attempt, injury	New or worsened psychiatric symptoms
Aripiprazole	3	676	39	1	1	1	2
Olanzapine	0	NA	NA	NA	NA	NA	NA
Ziprasidone	5	1436	124	3	2	9	57
Atomoxetine	0	NA	NA	NA	NA	NA	NA
Duloxetine	1	657	2	0	0	0	1
Sertraline	1	157	2	0	0	1	0
All Drugs	10	2926	167	4	3	11	60

Summary ID#4091

Clinical Study Summary: Study F1J-MC-HMAT Study Group B

Title of Study: Duloxetine Versus Placebo and Paroxetine in the Acute Treatment of Major Depression	
Investigator(s): This multicenter study included 20 principal investigators.	
Study Center(s): There were 22 study sites (two investigators had satellite sites) in the United States.	
Length of Study: 11 months Date first patient enrolled: 09 March 2000 Date last patient completed: 06 February 2001	**Phase of Development:** 3

Objectives: The primary objective of this study was to demonstrate that duloxetine 40 mg twice daily (BID) is superior to placebo in the acute treatment of patients with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)–defined major depressive disorder (MDD).

The secondary objectives of this study were:

- To compare the safety of duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine using information on discontinuation rates, treatment-emergent adverse events (TEAEs), discontinuation-emergent adverse events, laboratory analyses, vital signs, and electrocardiograms (ECGs).
- To compare the efficacy of duloxetine 40 mg BID with paroxetine as measured by a noninferiority test of mean 17-item Hamilton Depression Rating Scale ($HAMD_{17}$) total scores at Visit 8. Data from each of the two studies (HMAT Study Group A and Study Group B) will be combined for this comparison.
- To assess the efficacy of duloxetine 20 mg BID and duloxetine 40 mg BID compared with placebo as measured by response and remission rates.
- To compare the time to onset of action (defined as time to meeting responder criteria) of duloxetine 20 mg BID, duloxetine 40 mg BID, and paroxetine.
- To compare the efficacy of duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine on anxiety symptoms associated with depression as measured by mean endpoint scores on the Hamilton Anxiety Rating Scale (HAMA) and the anxiety subscale of the $HAMD_{17}$.
- To compare the efficacy of duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine as measured by mean endpoint scores (after adjusting for baseline differences) on the Clinical Global Impressions of Severity scale (CGI-Severity), the Montgomery and Asberg Depression Rating Scale (MADRS), $HAMD_{17}$ subfactor scores, and endpoint scores on the Patient's Global Impressions of Improvement scale (PGI-Improvement).
- To compare the efficacy of duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine on somatic complaints of pain using the Somatic Symptom Inventory scale (SSI) and Visual Analog Scales (VAS).
- To compare the impact of treatment with duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine on sexual functioning as measured by the Arizona Sexual Experiences Scale (ASEX).
- To compare the impact of treatment with duloxetine 20 mg BID, duloxetine 40 mg BID, placebo, and paroxetine on quality of life as measured by the Quality of Life in Depression Scale (QLDS), and on medical resource utilization and work productivity as measured by the Resource Utilization scale.

Study Design: Multicenter, parallel, double-blind, randomized, placebo- and active comparator-controlled study with blinded placebo lead-in and placebo lead-out. The protocol consisted of two identical studies conducted in parallel and reported separately (Study Group A and Study Group B). The study consisted of two study periods. Study Period I was the 1-week screening phase of the study, and Study Period II was an 11-week acute therapy phase in which patients were assessed weekly from Visit 2 (Week 0) to Visit 5 (Week 3) and every other week from Visit 5 (Week 3) to Visit 9 (Week 11). This study design employed double-blind, variable-duration placebo lead-in and lead-out periods to blind patients and investigators at the start and end of active therapy. Figure HMATb.1 illustrates the study design.
Number of Patients: Planned: 356 patients (89 per treatment group) Randomized: 86 Duloxetine 20 mg BID; 91 Duloxetine 40 mg BID ; 89 Placebo; 87 Paroxetine 20 mg QD. Completed: 55 Duloxetine 20 mg BID; 53 Duloxetine 40 mg BID; 52 Placebo; 49 Paroxetine 20 mg QD.
Diagnosis and Main Criteria for Inclusion: Male and female outpatients of at least 18 years of age with a primary diagnosis of MDD as defined by the DSM-IV, and confirmed by use of the Mini International Neuropsychiatric Interview (MINI). Patients were required to have a $HAMD_{17}$ total score ≥15 and a CGI-Severity total score ≥4 at both Visit 1 and Visit 2.
Test Product, Dose, and Mode of Administration: Duloxetine capsules, 20 mg; patients took 40 mg orally twice daily or 20 mg orally twice daily.
Duration of Treatment: Duloxetine: 8 weeks Paroxetine: 8 weeks Placebo: 11 weeks
Reference Therapy, Dose, and Mode of Administration: Paroxetine 20 mg capsules; patients took 20 mg orally once daily. Placebo capsules
Variables: Efficacy: The primary efficacy measure was the $HAMD_{17}$ total score. Secondary efficacy measures included $HAMD_{17}$ response rates (50% reduction from baseline to endpoint), $HAMD_{17}$ remission rates (endpoint score ≤7), time to sustained response, and time to sustained remission. Other secondary measures included the $HAMD_{17}$ subfactors and individual items, MADRS, CGI-Severity, PGI-Improvement, HAMA, Somatic Symptom Inventory (SSI) 26- and 28-item scale, and Visual Analog Scales (VAS) for pain. Safety: Safety was evaluated through the collection and reporting of discontinuation rates, TEAEs, discontinuation-emergent adverse events, laboratory analyses, vital signs, ECGs, and the ASEX. Health Outcomes: Health outcomes were evaluated using the QLDS scale and Health Resource Utilization scales. Health Resource Utilization results will not be reported in this synopsis.

Evaluation Methods:

Statistical:

The primary efficacy comparison was between duloxetine 40 mg BID and placebo, based on the likelihood-based repeated measures analysis. The terms in the repeated measure analysis model included treatment, visit, investigative site, baseline score, and the interactions of visit with treatment and baseline score. For secondary measures, an analysis of covariance (ANCOVA)/analysis of variance (ANOVA) model containing terms for treatment, investigator, and baseline score (no baseline score term in ANOVA model) was used for continuous variables. Categorical variables such as response and remission rates were evaluated using Fisher's exact test and the Cochran-Mantel-Haenszel (CMH) chi-square test with investigative site as strata. Time to event data, such as time to onset of action, were analyzed using the Kaplan-Meier method, and the treatment group differences were tested by the log-rank and Wilcoxon tests.

An intent-to-treat (ITT) principle was applied in all efficacy and safety analyses. For all total scores calculated from individual items, if any of the individual items was missing, the corresponding total score was considered missing. Sites with fewer than 8 randomly assigned patients with baseline and at least one postbaseline (Visit 4 to Visit 8) $HAMD_{17}$ total score were pooled. If this resulted in a pooled site with fewer than 8 patients, these patients were pooled with the next smallest site. For efficacy and safety analyses, treatment group differences were tested at a 2-sided significance level of 0.05.

The planned sample size (356 patients) provides 83% power to detect a difference between the duloxetine 40 mg BID and placebo groups of 3.25 points in mean change from baseline to endpoint of the $HAMD_{17}$ total score, assuming a common standard deviation of 7.0, 90% of patients would provide at least one baseline and one postbaseline assessment, and using a two-sided test with α=0.05. Using data pooled from Study Group A and Study Group B, this sample size also provides 80% power to test the non-inferiority of duloxetine 40 mg BID compared with paroxetine using a one-sided 97.5% confidence interval and an equivalence limit of –2.2 for mean $HAMD_{17}$ scores.

Summary:

Disposition/Demographics (Table HMATb.1): A total of 353 patients were randomly assigned and enrolled into the study. Of these, 209 patients completed the acute therapy phase (placebo, n=52; duloxetine 20 mg BID, n=55; duloxetine 40 mg BID, n=53; paroxetine 20 mg QD, n=49) and 206 completed the entire study. The percentages of patients who discontinued for any reason during the acute therapy phase were similar among the four treatment groups. No statistically significant differences were observed among treatment groups with regard to age, gender, origin, or height. Patients had a mean age of approximately 40 years, with the majority being Caucasian and female.

Efficacy Measures (Tables HMATb.2, Table HMATb.3)**:** Patients treated with duloxetine at both doses (20 mg BID and 40 mg BID) had statistically significantly greater improvement in the primary efficacy measure ($HAMD_{17}$ total score) compared with placebo-treated patients, by repeated measures analysis. Paroxetine-treated patients did not differ statistically significantly from the placebo group on this measure. Mean change analyses revealed the same results. Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement in scores on the primary efficacy measure ($HAMD_{17}$ total score) compared with paroxetine-treated patients at endpoint.

Patients treated with duloxetine 40 mg BID met the criteria for treatment response and remission at endpoint statistically significantly more frequently than did patients treated with placebo. Patients treated with either duloxetine 40 mg BID or paroxetine had statistically significantly shorter time to first response than did patients treated with placebo.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the $HAMD_{17}$ subfactor scores of Anxiety/Somatization, Core Factor, Maier, and Retardation as compared with placebo-treated patients.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the MADRS total score compared with placebo-treated patients, by repeated measures analysis. Mean change analysis revealed the same result. Duloxetine 20 mg BID, paroxetine- and placebo-treated patients did not differ statistically significantly on this measure.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the HAMA scale compared with placebo-treated patients (despite the fact that this trial excluded patients with primary anxiety disorders). Mean change analyses revealed the same result. Paroxetine- and placebo-treated patients did not differ statistically significantly on this measure.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the Visual Analog Scale (VAS) for overall pain severity compared with placebo-treated patients, and showed marginally statistically significantly greater improvement on the VAS for amount of time in pain while awake. Mean change analyses revealed the same results.

Patients treated with duloxetine 40 mg BID showed statistically significantly greater improvement on the Quality of Life in Depression Scale (QLDS), and showed a statistically significantly greater percentage of patients with reductions in the types of health care providers visited and the number of visits to health care providers, compared with placebo-treated patients.

There were statistically significantly fewer discontinuations due to perceived lack of efficacy for patients treated with both doses of duloxetine compared with placebo-treated patients.

Using 2.2 as the noninferiority margin, it is shown that duloxetine 40 mg BID treatment was noninferior to paroxetine treatment using either repeated measure analysis or mean change analysis. In addition, even when using a more stringent noninferiority margin than 2.2 (namely, using one-half of the absolute gain of paroxetine over placebo), it remains true that duloxetine 40 mg BID treatment was noninferior to paroxetine treatment using repeated measures analysis.

Safety — Acute Therapy Phase:

Deaths/Serious Adverse Events/Discontinuations Due to Adverse Events: No patients died during this study. Two patients experienced serious adverse events postrandomization. One patient receiving duloxetine 40 mg BID had an accidental injury falling from a horse, suffering a concussion and a subsequent seizure. One patient receiving paroxetine relapsed into alcohol abuse, suffered alcohol withdrawal symptoms, and was admitted for detoxification. In the acute therapy phase 40 (11.3%) of 353 discontinued due to an adverse event. There were no statistically significant differences among treatment groups with respect to adverse events reported as a reason for discontinuation in the acute therapy phase. The percentages of patients who discontinued for any reason were similar among the four treatment groups.

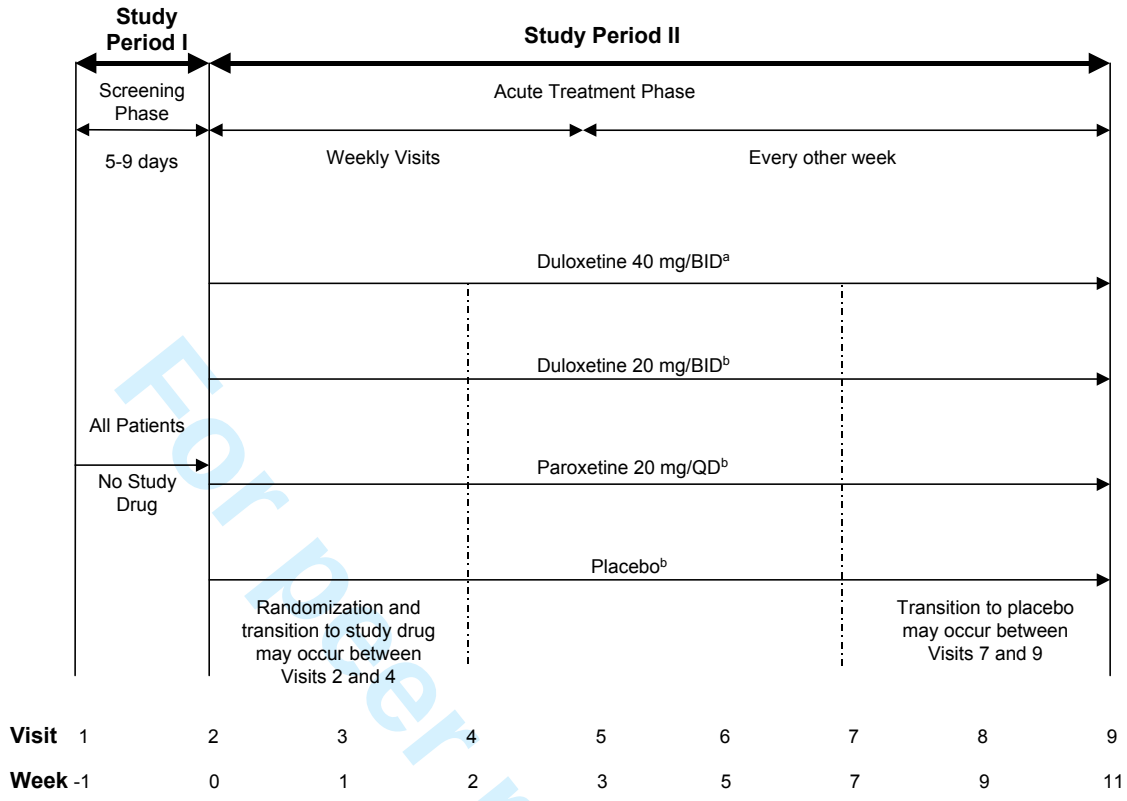

Figure HMAT.1. Illustration of study design for Protocol F1J-MC-HMAT.

Table HMATb.1. Patient Characteristics at Baseline
All Randomized Patients

Variable	PLACEBO (N=89)	DLX20BID (N=86)	DLX40BID (N=91)	PRX20QD (N=87)	Total (N=353)	p-Value
AGE: YRS						
No. Patients	89	86	91	87	353	.949**
Mean	40.14	40.69	40.89	40.25	40.50	
Median	41.28	40.05	40.83	39.25	40.29	
Standard Dev.	12.94	10.04	11.90	11.02	11.50	
Minimum	20.07	20.56	18.20	19.18	18.20	
Maximum	78.21	70.60	68.87	64.02	78.21	
HEIGHT: CM (Visit: 1)						
No. Patients	89	85	91	87	352	.556**
Mean	170.84	170.66	169.45	169.19	170.03	
Median	170.18	167.64	167.64	170.18	167.64	
Standard Dev.	9.69	9.66	10.72	9.79	9.97	
Minimum	152.40	152.40	139.70	149.86	139.70	
Maximum	198.12	200.66	195.58	193.04	200.66	
Unspecified	0	1	0	0	1	
WEIGHT: KG (Visit: 1)						
No. Patients	88	86	90	87	351	.071**
Mean	80.22	81.61	82.19	88.75	83.18	
Median	77.86	78.09	81.95	79.00	79.00	
Standard Dev.	18.93	20.33	20.87	28.97	22.74	
Minimum	45.40	51.76	43.58	45.40	43.58	
Maximum	153.91	165.26	155.72	194.31	194.31	
Unspecified	1	0	1	0	2	

Table HMATb.1. Patient Characteristics at Baseline
All Randomized Patients (concluded)

Variable	PLACEBO (N=89)	DLX20BID (N=86)	DLX40BID (N=91)	PRX20QD (N=87)	Total (N=353)	p-Value
ORIGIN: NO. (%)						
No. Patients	89	86	91	87	353	.270*
African Descent	8 (9.0)	4 (4.7)	5 (5.5)	9 (10.3)	26 (7.4)	
Western Asian	0	0	0	2 (2.3)	2 (0.6)	
Caucasian	74 (83.1)	72 (83.7)	77 (84.6)	64 (73.6)	287 (81.3)	
East/Southeast A	1 (1.1)	0	0	0	1 (0.3)	
Hispanic	6 (6.7)	9 (10.5)	9 (9.9)	12 (13.8)	36 (10.2)	
Other	0	1 (1.2)	0	0	1 (0.3)	
GENDER: NO. (%)						
No. Patients	89	86	91	87	353	.633*
Female	57 (64.0)	48 (55.8)	56 (61.5)	56 (64.4)	217 (61.5)	
Male	32 (36.0)	38 (44.2)	35 (38.5)	31 (35.6)	136 (38.5)	

Output stored as RMP.F1JO.HMAT.FINALB(DE128006)
Data from RMP.SAS.F1JM.MCHMATSW.STUDYB
* Frequencies are analyzed using a Chi-Square test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=investigator and treatment.
XDES0001

Table HMATb.2. Summary of Efficacy and Health Outcome Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb

Variable	Treatment Group: Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	p-Value: Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
$HAMD_{17}$ Total Score	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	17.19 (5.11)	18.63 (5.85)	18.06 (4.52)	17.65 (5.13)			
Mean Change (SD)	–4.16 (6.42)	–7.17 (7.97)	–7.72 (7.67)	–6.06 (8.12)	p=.022	p=.003	p=.150
LS Mean Change (SE)	–4.99 (0.81)	–7.42 (0.80)	–8.61 (0.81)[a]	–6.22 (0.82)	p=.034	p=.002	p=.285
$HAMD_{17}$ Response Rate	n=88	n=84	n=86	n=84			
Responders n (%)	27 (31%)	37 (44%)	44 (51%)	34 (40%)	.083	.009	.204
$HAMD_{17}$ Remission Rate	n=88	n=84	n=86	n=84			
Remitters n (%)	26 (30%)	29 (35%)	43 (50%)	31 (37%)	.516	.008	.334
$HAMD_{17}$ Subscale – Core	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	7.43 (2.64)	8.05 (2.53)	7.36 (2.14)	7.65 (2.43)			
Mean Change (SD)	–2.02 (3.39)	–3.37 (3.53)	–3.40 (3.14)	–3.00 (3.87)	p=.023	p=.008	p=.110
LS Mean Change (SE)	–2.64 (0.39)	–3.66 (0.38)	–4.00 (0.39)	–3.24 (0.39)	p=.060	p=.013	p=.271
$HAMD_{17}$ Subscale – Maier	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	9.26 (3.00)	9.88 (3.01)	9.47 (2.28)	9.33 (2.64)			
Mean Change (SD)	–2.53 (3.56)	–4.04 (4.25)	–4.30 (3.90)	–3.75 (4.33)	p=.028	p=.004	p=.057
LS Mean Change (SE)	–3.06 (0.44)	–4.18 (0.43)	–4.79 (0.44)	–4.03 (0.44)	p=.068	p=.005	p=.115

Table HMATb.2. Summary of Efficacy and Health Outcome Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (continued)

Variable	Treatment Group: Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	p-Value: Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
$HAMD_{17}$ Subscale – Anxiety/Somatization	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	5.48 (2.12)	6.04 (2.52)	6.07 (1.82)	5.85 (2.41)			
Mean Change (SD)	–1.06 (2.49)	–2.17 (3.08)	–2.79 (2.72)	–2.13 (3.23)	p=.046	p=<.001	p=.040
LS Mean Change (SE)	–1.38 (0.29)	–2.11 (0.28)	–2.92 (0.28)[a]	–2.11 (0.29)	p=.066	p=<.001	p=.069
$HAMD_{17}$ Subscale – Retardation/Somatization	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	6.38 (1.97)	6.96 (2.11)	6.34 (1.75)	6.81 (1.95)			
Mean Change (SD)	–1.80 (2.84)	–2.80 (3.03)	–2.63 (2.80)	–2.45 (3.15)	p=.047	p=.053	p=.263
LS Mean Change (SE)	–2.32 (0.32)	–3.08 (0.32)	–3.22 (0.32)	–2.59 (0.33)	p=.092	p=.046	p=.546
$HAMD_{17}$ Subscale – Sleep	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	2.67 (1.87)	2.76 (1.86)	2.85 (1.82)	2.54 (1.85)			
Mean Change (SD)	–0.81 (1.91)	–1.05 (2.04)	–1.02 (2.29)	–0.69 (2.16)	p=.485	p=.769	p=.827
LS Mean Change (SE)	–0.84 (0.21)	–1.04 (0.20)	–1.14 (0.21)	–0.65 (0.21)	p=.483	p=.303	p=.503

Approved by Lilly 16 November 2004

Table HMATb.2. Summary of Efficacy and Health Outcome Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (continued)

	Treatment Group				p-Value		
Variable	**Placebo**	**Dulox 20 BID**	**Dulox 40 BID**	**Parox 20 QD**	**Dulox 20 vs placebo**	**Dulox 40 vs placebo**	**Parox 20 vs placebo**
$HAMD_{17}$ Item #1 Score	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	2.32 (0.89)	2.52 (0.80)	2.24 (0.77)	2.37 (0.79)			
Mean Change (SD)	–0.67 (1.24)	–1.08 (1.19)	–0.95 (1.02)	–0.96 (1.31)	p=.054	p=.065	p=.122
LS Mean Change (SE)	–0.89 (0.13)	–1.15 (0.13)	–1.16 (0.13)	–1.11 (0.13)	p=.174	p=.152	p=.255
MADRS	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	22.72 (8.00)	24.44 (8.05)	22.58 (6.21)	23.07 (7.51)			
Mean Change (SD)	–5.75 (9.19)	–9.11 (11.50)	–8.99 (10.08)	–8.51 (11.91)	p=.082	p=.029	p=.105
LS Mean Change (SE)	–7.43 (1.15)	–9.37 (1.14)	–10.73 (1.16)	–9.01 (1.17)	p=.227	p=.042	p=.331
CGI-Severity	n=88	n=84	n=87	n=85			
Mean Baseline (SD)	4.11 (0.73)	4.19 (0.80)	4.10 (0.51)	4.02 (0.62)			
Mean Change (SD)	–0.88 (1.21)	–1.19 (1.38)	–1.20 (1.26)	–1.06 (1.39)	p=.135	p=.078	p=.262
LS Mean Change (SE)	–1.10 (0.15)	–1.36 (0.15)	–1.42 (0.16)	–1.25 (0.16)	p=.242	p=.153	p=.507

Table HMATb.2. Summary of Efficacy and Health Outcome Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (concluded)

	Treatment Group				p-Value		
Variable	Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
PGI-Improvement	n=88	n=84	n=86	n=85			
Mean Baseline (SD)	n/a	n/a	n/a	n/a			
Endpoint Mean (SD)	3.24 (1.41)	2.93 (1.31)	2.86 (1.47)	2.99 (1.44)	p=.162	p=.079	p=.253
Endpoint LS Mean (SE)	2.87 (0.15)	2.74 (0.15)	2.52 (0.15)	2.80 (0.15)	p=.522	p=.093	p=.743
HAMA	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	14.48 (5.33)	15.25 (5.86)	14.88 (4.87)	14.49 (5.76)			
Mean Change (SD)	–3.49 (5.32)	–5.13 (6.74)	–5.86 (7.14)	–4.60 (7.36)	p=.149	p=.019	p=.257
LS Mean Change (SE)	–4.33 (0.69)	–5.45 (0.68)	–6.57 (0.69)	–5.23 (0.69)	p=.238	p=.020	p=.349
QLDS	n=80	n=76	n=78	n=72			
Mean Baseline (SD)	15.21 (7.32)	19.92 (7.37)	17.22 (7.67)	17.60 (8.49)			
Mean Change (SD)	–4.30 (8.21)	–9.29 (8.61)	–8.55 (9.39)	–7.96 (10.26)	p=.069	p=.023	p=.084
LS Mean Change (SE)	–7.87 (1.07)	–8.90 (1.04)	–10.76 (1.05)	–9.85 (1.04)	p=.483	p=.050	p=.178

Abbreviations: CGI-Severity = Clinical Global Impressions of Severity; HAMA = Hamilton Anxiety Rating Scale; $HAMD_{17}$ = 17-Item Hamilton Depression Rating Scale; MADRS = Montgomery and Asberg Depression Rating Scale; PGI-Improvement = Patient's Global Impressions of Improvement; Dulox 20 BID = duloxetine 20 mg twice daily; Dulox 40 BID = duloxetine 40 mg twice daily; Parox 20 QD = paroxetine 20 mg once daily; QLDS = Quality of Life in Depression Scale; SD = standard deviation; SE = standard error.

Note: n = the number of patients who had a baseline score and at least one nonmissing postbaseline score for that particular variable

Note: "n/a" in Global Impressions of Improvement scales indicates that a baseline score is not collected in this type of scale

Note: Mean Change – Data from mean change analysis

Note: LS Mean Change – Data from repeated measures analysis

[a] Result was statistically significant (p≤.05) compared with paroxetine 20 mg QD

Table HMATb.3. Summary of Somatic and Pain Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb

Variable	Treatment Group				p-Value		
	Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
SSI 26-Item Average	n=88	n=82	n=86	n=85			
Mean Baseline (SD)	1.68 (0.55)	1.71 (0.51)	1.71 (0.55)	1.71 (0.47)			
Mean Change (SD)	–0.13 (0.47)	–0.13 (0.35)	–0.17 (0.46)	–0.17 (0.47)	p=.700	p=.875	p=.732
LS Mean Change (SE)	–0.18 (0.05)	–0.15 (0.05)	–0.22 (0.05)	–0.22 (0.05)	p=.620	p=.621	p=.540
SSI 28-Item Average	n=88	n=82	n=86	n=85			
Mean Baseline (SD)	1.69 (0.56)	1.72 (0.51)	1.74 (0.57)	1.72 (0.49)			
Mean Change (SD)	–0.13 (0.47)	–0.13 (0.35)	–0.19 (0.46)	–0.17 (0.47)	p=.703	p=.640	p=.740
LS Mean Change (SE)	–0.18 (0.05)	–0.15 (0.05)	–0.24 (0.05)	–0.22 (0.05)	p=.636	p=.409	p=.581
VAS-Severity of Overall Pain	n=88	n=84	n=86	n=85			
Mean Baseline (SD)	24.18 (25.99)	27.02 (25.39)	25.55 (22.83)	22.22 (22.48)			
Mean Change (SD)	–3.20 (27.17)	–6.44 (23.30)	–10.34 (22.52)	–8.06 (20.26)	p=.710	p=.048	p=.071
LS Mean Change (SE)	–4.09 (2.49)	–5.08 (2.42)	–11.44 (2.49)	–9.63 (2.51)	p=.771	p=.035	p=.113

Table HMATb.3. Summary of Somatic and Pain Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (continued)

	Treatment Group				p-Value		
Variable	Placebo	Dulox 20 BID	Dulox 40 BID	Parox 20 QD	Dulox 20 vs placebo	Dulox 40 vs placebo	Parox 20 vs placebo
VAS-Severity of Headaches	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	23.68 (28.58)	20.63 (23.70)	22.42 (23.30)	16.05 (20.63)			
Mean Change (SD)	–6.17 (25.39)	–3.36 (22.70)	–7.99 (24.03)	–3.40 (23.08)	p=.677	p=.470	p=.603
LS Mean Change (SE)	–6.25 (2.30)	–5.56 (2.23)	–7.90 (2.30)	–6.83 (2.32)	p=.828	p=.607	p=.859
VAS-Severity of Back Pain	n=88	n=84	n=86	n=85			
Mean Baseline (SD)	17.23 (22.76)	22.31 (26.11)	20.19 (24.61)	15.87 (18.07)			
Mean Change (SD)	–1.19 (25.30)	–6.88 (21.83)	–8.31 (24.05)	–3.36 (20.01)	p=.414	p=.094	p=.387
LS Mean Change (SE)	–2.48 (2.41)	–5.06 (2.35)	–7.67 (2.41)	–4.19 (2.43)	p=.439	p=.124	p=.612
VAS-Severity of Shoulder Pain	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	14.64 (23.56)	12.65 (19.58)	15.98 (22.24)	13.68 (22.73)			
Mean Change (SD)	–2.40 (20.09)	–2.07 (19.53)	–7.97 (21.61)	–2.71 (22.95)	p=.899	p=.081	p=.907
LS Mean Change (SE)	–2.34 (2.26)	–2.98 (2.19)	–5.67 (2.26)	–0.82 (2.26)	p=.837	p=.292	p=.631

Table HMATb.3. Summary of Somatic and Pain Measures
Mean Change from Baseline to Endpoint/Last Observation
All Randomized Patients
Acute Therapy Phase F1J-MC-HMATb (concluded)

	Treatment Group				p-Value		
Variable	**Placebo**	**Dulox 20 BID**	**Dulox 40 BID**	**Parox 20 QD**	**Dulox 20 vs placebo**	**Dulox 40 vs placebo**	**Parox 20 vs placebo**
VAS-Interference with Daily Activities	n=88	n=84	n=86	n=85			
Mean Baseline (SD)	17.14 (25.42)	19.52 (24.66)	17.00 (21.00)	15.62 (20.91)			
Mean Change (SD)	–3.38 (26.49)	–1.94 (26.44)	–4.90 (25.39)	–3.29 (20.77)	p=.261	p=.687	p=.915
LS Mean Change (SE)	–4.31 (2.53)	–0.57 (2.45)	–6.79 (2.52)	–4.24 (2.53)	p=.281	p=.482	p=.983
VAS-Pain While Awake	n=88	n=84	n=86	n=84			
Mean Baseline (SD)	25.73 (28.05)	34.93 (32.52)	29.23 (27.28)	28.30 (30.51)			
Mean Change (SD)	–1.95 (30.33)	–8.18 (31.49)	–10.99 (32.23)	–8.10 (32.52)	p=.787	p=.078	p=.269
LS Mean Change (SE)	–2.43 (3.32)	–2.70 (3.23)	–11.36 (3.31)	–6.02 (3.33)	p=.952	p=.055	p=.440

Abbreviations: Dulox 20 BID = duloxetine 20 mg twice daily; Dulox 40 BID = duloxetine 40 mg twice daily; Parox 20 QD = paroxetine 20 mg once daily; SSI = Somatic Symptom Inventory; VAS = Visual Analog Scales

Note: n = the number of patients who had a baseline score and at least one nonmissing postbaseline score for that particular variable

Note: Mean Change – Data from mean change analysis

Note: LS Mean Change – Data from repeated measures analysis

Table HMATb.4. Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2 Percent
All Randomized Patients
Acute Therapy Phase

	PLACEBO N=89 n(%)	DLX20BID N=86 n(%)	DLX40BID N=91 n(%)	PRX20QD N=87 n(%)	Total N=353 n(%)	p-Values* Overall	1vs2	1vs3	1vs4	2vs3	2vs4	3vs4
PATIENTS WITH >= 1 TESS	61(68.5)	73(84.9)	76(83.5)	76(87.4)	286(81.0)	.009	.013	.023	.003	.839	.666	.528
NAUSEA	2(2.2)	19(22.1)	23(25.3)	14(16.1)	58(16.4)	<.001	<.001	<.001	.001	.724	.339	.143
HEADACHE	10(11.2)	12(14.0)	17(18.7)	10(11.5)	49(13.9)	.470	.652	.211	1.00	.423	.655	.213
INSOMNIA	5(5.6)	15(17.4)	18(19.8)	7(8.0)	45(12.7)	.008	.017	.006	.564	.705	.072	.031
RHINITIS	15(16.9)	7(8.1)	5(5.5)	7(8.0)	34(9.6)	.075	.110	.018	.110	.558	1.00	.560
SOMNOLENCE	2(2.2)	15(17.4)	10(11.0)	7(8.0)	34(9.6)	.005	<.001	.033	.098	.281	.072	.613
DIZZINESS	5(5.6)	4(4.7)	15(16.5)	9(10.3)	33(9.3)	.032	1.00	.031	.278	.014	.248	.276
DRY MOUTH	3(3.4)	9(10.5)	14(15.4)	7(8.0)	33(9.3)	.042	.077	.009	.209	.377	.611	.165
DIARRHEA	7(7.9)	7(8.1)	8(8.8)	10(11.5)	32(9.1)	.851	1.00	1.00	.454	1.00	.611	.624
CONSTIPATION	3(3.4)	7(8.1)	8(8.8)	12(13.8)	30(8.5)	.095	.207	.212	.015	1.00	.331	.346
PAIN	10(11.2)	6(7.0)	3(3.3)	6(6.9)	25(7.1)	.230	.434	.047	.433	.319	1.00	.322
SWEATING	0(0.0)	8(9.3)	11(12.1)	6(6.9)	25(7.1)	.003	.003	<.001	.013	.631	.590	.310
ASTHENIA	2(2.2)	8(9.3)	9(9.9)	4(4.6)	23(6.5)	.102	.055	.058	.441	1.00	.248	.250
DYSPEPSIA	6(6.7)	3(3.5)	6(6.6)	6(6.9)	21(5.9)	.743	.497	1.00	1.00	.498	.496	1.00
BACK PAIN	6(6.7)	7(8.1)	3(3.3)	3(3.4)	19(5.4)	.408	.779	.327	.497	.202	.211	1.00
ANOREXIA	1(1.1)	4(4.7)	10(11.0)	3(3.4)	18(5.1)	.028	.205	.009	.365	.164	.720	.082
VASODILATATION	2(2.2)	7(8.1)	6(6.6)	2(2.3)	17(4.8)	.158	.096	.278	1.00	.778	.099	.279
ABDOMINAL PAIN	2(2.2)	6(7.0)	4(4.4)	3(3.4)	15(4.2)	.457	.164	.682	.680	.527	.329	1.00
COUGH INCREASED	5(5.6)	3(3.5)	3(3.3)	4(4.6)	15(4.2)	.886	.720	.494	1.00	1.00	1.00	.716
LIBIDO DECREASED	1(1.1)	4(4.7)	7(7.7)	3(3.4)	15(4.2)	.163	.205	.064	.365	.537	.720	.331
VOMITING	1(1.1)	6(7.0)	5(5.5)	3(3.4)	15(4.2)	.203	.061	.211	.365	.762	.329	.721
MYALGIA	4(4.5)	4(4.7)	3(3.3)	3(3.4)	14(4.0)	.933	1.00	.719	1.00	.714	.720	1.00
NERVOUSNESS	2(2.2)	4(4.7)	5(5.5)	1(1.1)	12(3.4)	.355	.438	.444	1.00	1.00	.211	.211
AMBLYOPIA	1(1.1)	1(1.2)	6(6.6)	3(3.4)	11(3.1)	.159	1.00	.118	.365	.119	.621	.497
ANORGASMIA	0(0.0)	4(4.7)	4(4.4)	3(3.4)	11(3.1)	.174	.056	.121	.119	1.00	.720	1.00
ANXIETY	0(0.0)	4(4.7)	3(3.3)	4(4.6)	11(3.1)	.172	.056	.246	.058	.714	1.00	.716
PARESTHESIA	4(4.5)	1(1.2)	2(2.2)	4(4.6)	11(3.1)	.485	.368	.441	1.00	1.00	.368	.436
ACCIDENTAL INJURY	0(0.0)	5(5.8)	2(2.2)	3(3.4)	10(2.8)	.091	.027	.497	.119	.268	.496	.677
PHARYNGITIS	5(5.6)	2(2.3)	1(1.1)	2(2.3)	10(2.8)	.380	.444	.116	.444	.612	1.00	.615
ABNORMAL DREAMS	0(0.0)	2(2.3)	2(2.2)	5(5.7)	9(2.5)	.119	.240	.497	.028	1.00	.443	.270

(1) = PLACEBO, (2) = DLX20BID, (3) = DLX40BID, (4) = PRX20QD
*p-Values are from Fisher's Exact test.

Table HMATb.4. Treatment-Emergent Adverse Events with Incidence Greater than or Equal to 2 Percent
All Randomized Patients
Acute Therapy Phase (concluded)

	PLACEBO N=89 n(%)	DLX20BID N=86 n(%)	DLX40BID N=91 n(%)	PRX20QD N=87 n(%)	Total N=353 n(%)	p-Values* Overall	1vs2	1vs3	1vs4	2vs3	2vs4	3vs4
ABNORMAL EJACULATION	1(1.1)	2(2.3)	2(2.2)	4(4.6)	9(2.5)	.539	.616	1.00	.208	1.00	.682	.436
IMPOTENCE	0(0.0)	4(4.7)	2(2.2)	3(3.4)	9(2.5)	.165	.056	.497	.119	.434	.720	.677
TREMOR	1(1.1)	3(3.5)	2(2.2)	3(3.4)	9(2.5)	.682	.362	1.00	.365	.675	1.00	.677
FLATULENCE	1(1.1)	2(2.3)	1(1.1)	4(4.6)	8(2.3)	.424	.616	1.00	.208	.612	.682	.203
PALPITATION	2(2.2)	2(2.3)	2(2.2)	2(2.3)	8(2.3)	1.000	1.00	1.00	1.00	1.00	1.00	1.00
RASH	3(3.4)	1(1.2)	4(4.4)	0(0.0)	8(2.3)	.195	.621	1.00	.246	.369	.497	.121
TINNITUS	1(1.1)	4(4.7)	2(2.2)	1(1.1)	8(2.3)	.436	.205	1.00	1.00	.434	.211	1.00
NECK PAIN	0(0.0)	4(4.7)	3(3.3)	0(0.0)	7(2.0)	.031	.056	.246		.714	.059	.246
PRURITUS	2(2.2)	2(2.3)	1(1.1)	2(2.3)	7(2.0)	.881	1.00	.619	1.00	.612	1.00	.615
THINKING ABNORMAL	0(0.0)	1(1.2)	5(5.5)	1(1.1)	7(2.0)	.067	.491	.059	.494	.212	1.00	.211
TWITCHING	1(1.1)	3(3.5)	2(2.2)	1(1.1)	7(2.0)	.630	.362	1.00	1.00	.675	.368	1.00
URINARY FREQUENCY	0(0.0)	3(3.5)	2(2.2)	2(2.3)	7(2.0)	.398	.117	.497	.243	.675	.682	1.00

Table HMATb.5. Laboratory Data - Chemistry Analytes
Analytes with Statistically Significant Mean Change From Baseline to Endpoint Values
All Randomized Patients
Acute Therapy Phase

				Baseline		Change to Endpoint		p-Values	
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)	Pair-wse*2
AST	U/L	PLACEBO	86	24.29	10.86	-2.05	10.11	.008	
		DLX20BID	81	22.68	7.44	3.17	10.60	(.475)	.001
		DLX40BID	81	22.67	10.21	1.25	8.03		.010
		PRX20QD	78	23.54	10.55	1.47	10.88		.015
ALT	U/L	PLACEBO	86	27.73	20.40	-3.56	13.73	.002	
		DLX20BID	81	25.48	15.69	4.15	18.93	(.480)	.004
		DLX40BID	81	24.37	17.50	3.86	13.69		<.001
		PRX20QD	78	28.51	20.92	-0.53	15.77		.070
CPK	U/L	PLACEBO	86	192.0	673.6	-55.6	427.5	.013	
		DLX20BID	81	126.6	89.0	30.9	115.1	(.813)	.040
		DLX40BID	81	123.8	101.5	-6.7	129.3		.599
		PRX20QD	78	111.0	63.8	31.8	173.0		.039
ALKPH	U/L	PLACEBO	86	68.6	20.4	-1.4	9.1	.049	
		DLX20BID	81	69.7	19.5	3.9	12.8	(.585)	.013
		DLX40BID	81	70.1	18.2	2.4	9.2		.019
		PRX20QD	78	72.5	23.4	0.9	14.0		.153
CALC	mmol/L	PLACEBO	86	2.397	0.111	-0.035	0.126	.009	
		DLX20BID	81	2.379	0.112	-0.006	0.148	(.280)	.273
		DLX40BID	81	2.398	0.120	-0.003	0.144		.193
		PRX20QD	78	2.357	0.102	0.032	0.110		<.001
SODIUM	mmol/L	PLACEBO	86	141.7	2.1	-1.2	2.8	.020	
		DLX20BID	81	141.5	2.2	-0.4	2.9	(.554)	.079
		DLX40BID	81	141.5	2.7	-0.2	3.3		.014
		PRX20QD	78	141.2	2.4	0.2	3.0		.004
UR AC	umol/L	PLACEBO	86	288.8	87.8	1.0	43.6	.145	
		DLX20BID	81	314.4	82.8	-1.0	48.8	(.810)	.262
		DLX40BID	81	304.9	84.1	-17.1	47.8		.022
		PRX20QD	78	300.8	81.5	-5.5	48.3		.150
T.BILI	umol/L	PLACEBO	86	6.8	6.0	0.9	2.9	.016	
		DLX20BID	81	6.7	4.2	-0.0	3.6	(.808)	.017
		DLX40BID	81	7.1	5.6	-0.5	3.4		.008
		PRX20QD	78	6.2	3.7	0.6	2.9		.591

Output stored as RMP.F1JO.HMAT.FINALB(LS604002)
Data from RMP.SAS.F1JM.MCHMATSW.STUDYB
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=investigator and treatment for the overall p-Value and model=investigator, treatment, and interaction for the interaction p-Value.
*2 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

Table HMATb.5. Laboratory Data - Chemistry Analytes
Analytes with Statistically Significant Mean Change From Baseline to Endpoint Values
All Randomized Patients
Acute Therapy Phase

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
AST	AST/SGOT
ALT	ALT/SGPT
CPK	CREATINE PHOSPHOKINASE
ALKPH	ALKALINE PHOSPHATASE
CALC	CALCIUM
SODIUM	SODIUM
UR AC	URIC ACID
T.BILI	BILIRUBIN, TOTAL

Table HMATb.6. Laboratory Data - Nonchemistry Analytes
Analytes with Statistically Significant Mean Change From Baseline to Endpoint Values
All Randomized Patients
Acute Therapy Phase

				Baseline		Change to Endpoint		p-Values		
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy (Int*1)	Pair-wse*2	Model
HCT	1	PLACEBO	79	0.4189	0.0394	-0.0090	0.0278	.067		RDUC1
		DLX20BID	76	0.4237	0.0364	0.0011	0.0240	(.613)	.019	
		DLX40BID	76	0.4233	0.0350	-0.0007	0.0259		.067	
		PRX20QD	67	0.4201	0.0398	-0.0057	0.0263		.634	
MCHC	mml/L-Fe	PLACEBO	79	21.0	1.1	0.1	1.1	.225		RDUC1
		DLX20BID	76	21.0	0.8	-0.2	1.0	(.736)	.047	
		DLX40BID	76	21.0	1.0	0.0	1.1		.583	
		PRX20QD	67	21.0	1.0	0.0	1.2		.628	
WBC	GI/L	PLACEBO	80	7.43	1.76	-0.31	1.21	.043		RDUC1
		DLX20BID	76	7.24	1.83	0.18	1.76	(.053)	.085	
		DLX40BID	77	7.85	2.23	-0.44	1.64		.359	
		PRX20QD	69	7.60	1.99	0.08	1.92		.245	
BANDS	GI/L	PLACEBO	80	0.000	0.000	0.000	0.000	*		FULL3
		DLX20BID	76	0.000	0.000	0.000	0.000	(*)	*	
		DLX40BID	77	0.000	0.000	0.000	0.000		*	
		PRX20QD	69	0.000	0.000	0.000	0.000		*	
POLYS	GI/L	PLACEBO	80	4.565	1.391	-0.284	1.084	.074		RDUC1
		DLX20BID	76	4.514	1.411	0.140	1.604	(.345)	.143	
		DLX40BID	77	4.942	1.731	-0.340	1.498		.511	
		PRX20QD	69	4.709	1.590	0.144	1.679		.126	
BASO	GI/L	PLACEBO	80	0.046	0.027	0.004	0.037	.034		RDUC1
		DLX20BID	76	0.049	0.027	0.003	0.025	(.420)	.400	
		DLX40BID	77	0.051	0.029	0.007	0.028		.178	
		PRX20QD	69	0.055	0.031	-0.005	0.045		.140	
MCV	fL	PLACEBO	79	89.0	5.4	-0.9	4.1	.055		RDUC1
		DLX20BID	76	89.6	5.1	0.9	3.8	(.879)	.006	
		DLX40BID	76	89.3	4.9	0.1	3.9		.226	
		PRX20QD	67	89.7	4.5	0.0	4.7		.157	
U-SPGR	NO UNITS	PLACEBO	54	1.0194	0.0082	-0.0007	0.0080	.013		RDUC2
		DLX20BID	52	1.0175	0.0075	0.0012	0.0087	(.335)	.212	
		DLX40BID	51	1.0177	0.0073	0.0039	0.0071		.001	
		PRX20QD	47	1.0197	0.0077	0.0021	0.0088		.060	
TSH	mU/L	PRX20QD	2	0.835	0.021	0.165	0.148			
CK-MB	ng/ml	PLACEBO	1	17.30		-4.20				
CKMBRI	ngL/Uml	PLACEBO	1	0.30		0.20				

Table HMATb.6. Laboratory Data - Nonchemistry Analytes
Analytes with Statistically Significant Mean Change From Baseline to Endpoint Values
All Randomized Patients
Acute Therapy Phase (concluded)

Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL3 - *1 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=inv., treatment, and interaction.
*2 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

RDUC1 - *1 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=investigator and treatment for the overall p-Value and model=investigator, treatment, and interaction for the interaction p-Value.
*2 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
Note: Each investigator has at least one patient in each treatment group.

RDUC2 - *1 Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks: PROC GLM model=investigator and treatment for the overall p-Value and model=investigator, treatment, and interaction for the interaction p-Value.
*2 Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.
Note: At least one investigator does not have patients in every treatment group.

*Note: Error sum of squares is equal to 0, thus no p-Values are computed.

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
MCHC	MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
U-SPGR	UA-SPECIFIC GRAVITY
TSH	THYROID STIM. HORMONE
CK-MB	CK-MB (IMX)
CKMBRI	CK-MB RELATIVE INDEX

Table HMATb.7. Summary of Vital Signs and Weight Change from Baseline to Endpoint All Randomized Patients Acute Therapy Phase

	Treatment Group			
Variable	Placebo	Dulox 20	Dulox 40	Paroxetine
Heart rate (bpm)	n=86	n=84	n=87	n=85
Mean baseline (SD)	73.50 (8.40)	71.75 (11.04)	71.02 (8.10)	71.20 (9.75)
Mean change (SD)	-1.66 (8.47)	0.75 (10.02)	2.02 (9.86)	-0.21 (10.03)
p-value (active vs placebo)		.172	.044	.524
Systolic blood pressure (mmHg)	n=86	n=84	n=87	n=85
Mean baseline (SD)	119.57 (12.95)	117.30 (11.12)	120.62 (13.05)	119.76 (15.36)
Mean change (SD)	-3.24 (12.50)	0.13 (11.85)	-0.18 (12.51)	0.42 (12.53)
p-value (active vs placebo)		.176	.098	.052
Diastolic blood pressure (mmHg)	n=86	n=84	n=87	n=85
Mean baseline (SD)	75.60 (9.57)	75.49 (8.87)	77.94 (9.43)	77.18 (10.17)
Mean change (SD)	-0.47 (8.61)	2.11 (9.04)	0.20 (7.33)	0.34 (9.97)
p-value (active vs placebo)		.045	.563	.527
Weight (kg)	n=87	n=84	n=86	n=85
Mean baseline (SD)	80.61 (18.87)	82.08 (20.31)	83.16 (20.95)	89.77 (79.45)
Mean change (SD)	0.47 (1.95)	-0.02 (2.08)	-0.60 (2.20)	-0.41 (2.63)
p-value (active vs placebo)		.149	.002	.010

Abbreviations: Dulox 20 BID = duloxetine 20 mg twice daily; Dulox 40 BID = duloxetine 40 mg twice daily; n = number of patients; Parox 20 QD = paroxetine 20 mg once daily; SD = standard deviation.

Table HMATb.8. Treatment-Emergent Abnormal Electrocardiograms
All Randomized Patients
Acute Therapy Phase

Therapy	N	Abnormal ECG n(%)	Fisher's Exact Pairwise p-Values vs. 1)	vs. 2)	vs. 3)
1)PLACEBO	56	10(18%)			
2)DLX20BID	48	11(23%)	.626		
3)DLX40BID	52	10(19%)	1.00	.807	
4)PRX20QD	48	10(21%)	.804	1.00	1.00

Fisher's Exact p-value overall = 0.9436
Program: RMP.F1JSHMAT.SASPGM.STUDYB(FQECGB1B) QCA70
Data: RMP.SAS.F1JM.MCHMATSW.STUDYB

Table HMATb.9. Summary of Arizona Sexual Experiences Scale
Change from Baseline to Endpoint
All Randomized Patients
Acute Therapy Phase

	Treatment Group			
Variable	Placebo	Dulox 20	Dulox 40	Paroxetine
ASEX Total Score	n=49	n=50	n=45	n=48
Mean baseline (SD)	16.20 (5.06)	15.90 (4.10)	16.36 (3.90)	15.96 (4.74)
Mean change (SD)	0.02 (3.94)	0.50 (3.88)	0.62 (4.80)	0.56 (5.13)
LS Means p-value (active vs placebo)		0.496	0.553	.728
ASEX sum of items 1 and 2	n=85	n=80	n=83	n=72
Mean baseline (SD)	7.53 (2.78)	7.55 (2.45)	7.58 (2.02)	7.60 (2.58)
Mean change (SD)	0.13 (2.06)	-0.24 (2.19)	0.02 (2.07)	-0.10 (2.29)
LS means p-value (active vs placebo)		.277	.850	.667

Abbreviations: ASEX = Arizona Sexual Experiences Scale; Dulox 20 BID = duloxetine 20 mg twice daily; Dulox 40 BID = duloxetine 40 mg twice daily; n = number of patients; Parox 20 QD = paroxetine 20 mg once daily; SD = standard deviation.

STROBE Statement

"Differences in Reporting Serious Adverse Events in Industry-Sponsored Clinical Trial Registries and Journal Articles on Antidepressant and Antipsychotic Drugs – A Cross-sectional Study"

	Page No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
	2	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	4-5	Explain the scientific background and rationale for the investigation being reported
Objectives	4-5	State specific objectives, including any prespecified hypotheses
Methods		
Study design	6-8	Present key elements of study design early in the paper
Setting	6-7	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6-7	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
Variables	8-9	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	6-9	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	8	Describe any efforts to address potential sources of bias
Study size	6-7	Explain how the study size was arrived at
Quantitative variables	8-9	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	9-10	(*a*) Describe all statistical methods, including those used to control for confounding
	n/a	(*b*) Describe any methods used to examine subgroups and interactions
	n/a	(*c*) Explain how missing data were addressed
	n/a	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	n/a	(*e*) Describe any sensitivity analyses

Results		
Participants	10, 24	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
	10, 24	(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	10-11, 25	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
	n/a	(b) Indicate number of participants with missing data for each variable of interest
Outcome data	11-13	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	11-13 n/a	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval).
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	14	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	15-17	Summarise key results with reference to study objectives
Limitations	18	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	15-19	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	18	Discuss the generalisability (external validity) of the study results
Other information		
Funding	20	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based