Are Regular Doses Of Citalopram For Depression Only Placebos? Meta-analysis And Meta-regression Analysis Of Pre-registration Clinical Trial Data

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Additional Files:
Prisma checklist
Prisma flow diagram
Letter from the Danish Medicinal Agency
Facsimile of original data
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Abstract

Background
We wanted to investigate whether unpublished, detailed data from before the time of the registration of the antidepressant drug citalopram would yield any additional information that should have been taken into consideration before licensing the drug.

Methods
Through an application to the Danish Ministry of Health and with help from the Danish Parliamentary Ombudsman, we obtained a copy of the pre-registration file from Lundbeck titled “Citalopram Clinical Expert Report” (dated 1988) along with the accompanying clinical-trial data. We found one published and one unpublished clinical trial of citalopram against placebo and nine studies in which citalopram was tested against active comparators in mentally depressed patients. Two of the studies were unpublished.

All 11 studies were randomized and double blinded. We selected data according to the principle of “last observation carried forward” and calculated the standardized mean differences between the groups and as well as the weighted averages for the two categories of studies using standard meta-analytic software. For the active comparator category against citalopram, we also performed a meta-regression with a daily drug dose as a covariate. In parallel, we explored the Norwegian Prescription Database to determine the actual citalopram-dose taken by most patients in recent years.

Results
The antidepressant effect of citalopram above 45 mg per day was similar to other antidepressant drugs (standardized mean difference 0.08; 95% confidence intervals -0.25 to 0.40, P=0.18). The effect was significantly better than that of a placebo (standardized mean difference 0.39 (0.11 to 0.67) P=0.007). However, with a dosage of less than 45 mg per day, the effect was significantly less than with the comparator drugs: -0.54 (-0.87 to 0.21) P=0.001. Meta-regression showed a positive correlation between citalopram dosage and effect with P-value 0.034. The median prescribed daily dose in Norwegian patients is 33 mg per day.

Conclusion
Pre-registrations studies with low doses showed lesser effects than comparator drugs, comparable to the effect of a placebo. Doses even below that are consumed by most patients, probably without any clinical effects. The recommended dose of 20 mg, which is the WHO-defined daily dose, was not tested in clinical trials before the registration of the drug.

Background
Because clinical-trial data submitted to regulatory agencies concerning the effects of drugs are, at the outset, confidential, they cannot be subjected to regular scrutiny by outside researchers. In one instance, the release of such data concerning paroxetine resulted in a suspicion that antidepressant drugs could precipitate suicidal activities [1]. This was later supported by other antidepressant-drug data concerning children and young adults [2]. In a meta-analysis of the adverse effects connected with paroxetine, surprisingly many symptoms, later on accepted as adverse effects, could be depicted already before the registration of the drug [3]. A comparison of the benefits and harms of second-generation antidepressants have recently been shown to be about equal among the drugs [4], although sertraline might be the best choice when taking also acceptability into consideration [5]. We wanted to investigate whether the detailed, unpublished data created before the time of registration of citalopram would yield any additional information. We therefore set forth to re-analyze the pre-registration data with a particular focus on the dose-effect relationship.

Methods
Through an application to the Danish Ministry of Health (Sundhedsministeriet) and with help from the Danish Parliamentary Ombudsman (Folketingets Ombudsmand), we obtained a copy of the
pre-registration file from Lundbeck titled “Citalopram Clinical Expert Report” (dated February 25th, 1988) along with accompanying clinical-trial data. The report we obtained was part of a new drug application for citalopram. The results from 49 studies were included. Among them, two with citalopram were tested against placebos and nine with citalopram tested against active comparators in mentally depressed patients. All 11 studies were randomized and double blinded.

We selected primarily Hamilton depression scale [6] results, otherwise we used results obtained with the MADRS scale [7]. We usedscores for the whole group of patients when available. In two reports, there were separate outcome data for endogenous and non-endogenous depression only, which we named a and b respectively in addition to the name of the first author. We used the score records according to the principle of “last observation carried forward.” As we did not have access to data necessary for a direct estimate, we used a surrogate method by obtaining the scores registered before there was any substantial drop in the study attendance of the patients, and we included the standard deviations of the observations when they were available. Otherwise, we used the average standard deviations of patient groups measured with the same depression scale.

Most of the data included in our main statistical analysis can be found in the additional file “Facsimile of original data.” In report no. 9, a and b, the numbers of patients assessable were 17 + 14 and 11 + 14 in the citalopram and mianserine groups, in endogenous and non-endogenous depressed patients, respectively. In report no. 11, there were 28 patients in each group. Other patient numbers are given in the additional file “Prisma 2009 Checklist” and “Prisma flow diagram.”

For the intention to treat analysis, we used the number of randomized patients given in Illustration 1.

From the Norwegian Prescription Database (NorPD), we obtained all records of redemptions of citalopram (ATC no. N06AB04) during the years 2004–2007. The ATC (Anatomical Therapeutic Chemical) number is given to the drug when it is registered by the Norwegian Medicinal Agency (Legemiddelverket). The NorPD uses the ATC code WHO. The seven-digit ATC classification has a hierarchical five-level structure starting with the broad indication (e.g. “N” for “Nervous system” [6]) and ending with a specific chemical substance.

In order to ensure we were studying patients with a certain degree of mental disturbances among them, we selected individuals who also had at least one prescription of an anxiolytic, hypnotic or sedative drug (ATC no. N06 B and C). To secure a high probability of continuous use of citalopram during the four years (and considering that – according to regulations – reimbursed drugs in Norway are prescribed maximally for three months with one redemption), we restricted the selection to the 1,208 patients who had between 16 and 25 redemptions of the drug during the observation period. Based on the means of the ten first redemptions for each patient, we then calculated the median dose for all patients and the corresponding 25th and 75th percentiles.

For the discussion section of the present article, we searched Medline with search words “citalopram/AD.PD,” “placebo.mp,” and “Depression disorder/Depression,” with limit to clinical trials. We also searched EMBASE, Cochrane and Forest Laboratories Clinical Trials Database and added studies from the reference lists of relevant literature.

**Statistical methods**

See the additional file “Facsimile of original data” for information concerning the effect scores used to perform the differences of means analysis. These data were fed into a tailor-made program for performing meta-analysis (Comprehensive Meta-analysis Version 2, from Biostat, Englewood, USA), which uses standard statistical procedures [9]. We filled in columns for the mean score, its standard deviation, and the number of patients in the citalopram group and in the comparator group. We added a column for correlation between before and after. We found a coefficient of correlation found to be 0.48, and standardized the effect analysis with standard deviations of the differences between values before and after. We found I2 to be 73.5 and performed random effect meta-analyses with the effects weighted with the inverse of their variances.

There were nine studies with active comparators against citalopram, two of which included two arms; i.e. there were 11 data sets altogether. We added a column for correlation between before and after, Pearson’s coefficient of correlation found to be 0.48, and standardized the effect analysis with standard deviations of the differences between values before and after. We found I2 to be 73.5 and performed random effect meta-analyses with the effects weighted with the inverse of their variances.

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**Results**

**Study characteristics**

Illustration 1 shows the characteristics of the 11 studies of citalopram tested against active comparators or a placebo, altogether 13 analyses due...
Discussion

We re-analyzed pre-registration data concerning citalopram with the intention of seeing whether the effects of 20 mg per day had been demonstrated in patients with depression. We found that no group of patients in the clinical trial program before registration in Denmark was ever subjected to that dose beyond an initial couple of weeks. Using functional magnetic resonance imaging, other authors have found that citalopram 20 mg per day versus a placebo for one week in healthy volunteers was associated with increased amygdala activation when they were exposed to happy faces [11]. Apparently, citalopram at this low dose is pharmacologically active. These authors sought but did not observe any mood changes. It is tempting, however, to hypothesize that depressed patients and those with other mental disorders experience some sort of relief when taking low dose citalopram. Otherwise it is difficult to explain its widespread use and popularity. We must, however, rely on the clinical trials that have been done. A fixed dose trial of 20 and 40 mg citalopram against a placebo was published by Montgomery et al in 1992 [12]. Only 40 mg was effective, but it was argued that these patients suffered from major depression and therefore needed a relatively high dose.

Evidence for an effect of low doses of citalopram was sought in another paper, this time in a general practice setting [13]. Here, a low dose (10–30 mg) and a high dose (20–60 mg) of citalopram were compared with imipramine as an active comparator. The outcome was remarkably similar in all three groups. However, without a control group, this result may also be interpreted as having no effect in any of the groups, which is not so farfetched because these patients suffered from minor depressions only. The excuse for omitting the control group was that citalopram had already been tested against a placebo in two studies and had shown effects. The authors did not mention that one of those studies had been performed with doses above 50 mg daily [14] or that the other had not, as already mentioned, found effects at the dosage of 20 mg daily [12].

In 1994, a meta-analysis of nine placebo-controlled, unpublished studies was undertaken [15]. It showed antidepressant effects of citalopram at daily doses of 20 mg and above, with a flat dose-response curve. It is problematic, however, that none were fixed-dose studies, and this might have introduced a bias. With flexible dosing, some patients given a low dose will show an effect by chance, and they will then stay on that dosage, while the non-responders will have their doses increased. Moreover, in these nine studies, only
“completers” were included in the final analysis. This introduces a second bias as it overrides the now-acknowledged principle of last observation carried forward. It is also problematic that the studies were not identified by the authors. Furthermore, in a summing up in the year 2000, another author informs the reader that up until that time there were 11 placebo-controlled studies with citalopram [16]. Among them, the authors says, were six studies (included in the above mentioned meta-analysis) that remained unpublished and three from the same meta-analysis that were published later on, as were two more recent studies. In the following, these five published studies are summarized, after which we report results from placebo-controlled studies made available in the period 2000–2010. First, as mentioned, one of the five published studies is included in our pre-registration meta-analysis [14]. This was a high-dosage study. Next on the list was Montgomery et al., 1992 [12], also already mentioned, showing no effect of 20 mg citalopram. Then there is Nyth et al., 1992 [17], with elderly outpatients who were allowed to have concomitant somatic disease with or without concomitant dementia. They used flexible dosing of up to 30 mg daily, not mentioning the average dose obtained. There were no difference between the numbers of patients showing a 50% reduction in their depression score and no difference in absolute scores after four weeks. After six weeks, there was a statistically significant difference. This is at variance with Roose et al., 2004. This later study found no differences in effects of 20–40 mg of citalopram daily in elderly patients compared with placebo [18]. Then there was a publication by Stahl, 2000, who used 60 mg of citalopram [19]. Finally, we have Feighner et al. 1999 [20], who found that with a fixed dose of 20 mg, the number of responders defined as having more than a 50% reduction in test score showed a statistically significant difference from the placebo group, the effect being less than with 40 mg of citalopram. This is a peculiar finding. For sure, some information in the data is lost with this method, and it does not agree with the differences in absolute test scores at the start and the study end. These differences were not explicitly reported in the publication, but it can be read from Figure 4 as approximately -9.5 for placebo and -10.3 for the drug. The difference between the differences was presented as not being statistically significant. This study was reanalyzed at a later date by manipulating the score system, and a statistical difference in one of the comparisons was found [21]. This difference showed an effects size of 0.27, which is far less than the minimal effect size of 0.5 considered to be of clinical interest [22].

During the last decade, the focus has been on comparing the enantiomer escitalopram with racemic citalopram and, according to a recent meta-analysis [23], three out of eleven such studies included a placebo group. One of them used 40 mg of citalopram [24]. Another study with flexible dosing and on average 24.4 mg of citalopram daily found test scores of -12.2 for the placebo and -13.7 for the drug [25]. The difference was noted as not significant statistically and, with a full scale of 60 points for the Montgomery Åsberg Depression Rating Scale, a difference of 1.5 points must be regarded as not clinically useful. Lastly, an unpublished study with flexible dosing of citalopram and on average 35.3 mg of citalopram [26] was reported with a non-statistically significant difference between the groups. In the same database, there is another observation of a fixed dosage of citalopram (40 mg) showing an effect against the placebo [26]. Altogether, the documentation for the clinical usefulness of 20 mg citalopram in depression is less than optimal. Probably many patients, even severely depressed ones, receive that dose. With other diagnoses, this might be sufficient. One can wonder why the preregistration documentation was accepted as a guidance of dosage and why 20 mg was accepted at all, as testing of this dose had not been included. One can also wonder what can be done to prevent such things from happening. It would probably be helpful if the data were submitted to regulatory agencies in a digital form ready for statistical analysis. One might suspect that in the present case, the data had not been re-analyzed by anyone at all, every conclusion presented in the new drug application being accepted as veracious. But our findings have further implications. In the meta-analysis comparing the s-isomer and racemic citalopram, the following mg-daily dosages of the latter were employed: 35.3, 20, 24.4, 20, 40, 40, 20–40, 20 and 10–40 [23]. The idea behind the comparison of the two enantiomers was that 10 mg of escitalopram should be equivalent to 20 mg of citalopram. But what if the presence of d-citalopram inhibits the action of s-citalopram? Our meta-analysis of preregistration studies, although primarily based on active drugs as controls, indicates that even 40 mg may not be optimal. This, together with our review of later clinical trials that used 20 mg of citalopram daily, opens up the possibility that there is an inhibition. This will invalidate the claim that escitalopram is a better drug than citalopram. Instead of exchanging one for the other, one could increase the dose of citalopram, which is obtainable in generic versions.
Conclusions

There is insufficient evidence that 20 mg daily of citalopram is clinically useful in patients with mental depression, probably not at all effective in major depression. Surprisingly, this dose was not tested before it was recommended. Two fixed-dose studies with 20 mg daily have been performed after the registration of the drug in Denmark. Neither study showed a statistically significant difference between the drug and the placebo in absolute depression scale scores. Increasing the recommended doses of citalopram is warranted. There are no good reasons for changing to escitalopram.

Acknowledgement

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Authors Contributions

NVA presented the problem and provided the data. MK extracted the data together with IA who suggested the statistical solution. All authors read and approved the final manuscript.

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References


26. Anonymous: A double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of flexible dosages of Lu 26-054 (escitalopram) and citalopram in outpatients with major depressive disorder.


Illustrations

Illustration 1

Characteristics of randomized clinical trials submitted with new drug application for citalopram

<table>
<thead>
<tr>
<th>Study name (no.) [Reference]</th>
<th>Report no.</th>
<th>No of patients randomized</th>
<th>Comparator (Test scale)</th>
<th>Diagnosis*</th>
<th>Observation length (weeks)</th>
<th>Mean dose at end-point (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen 1986a (79-03) [27]</td>
<td>4</td>
<td>43(41)</td>
<td>mianserine (Hamilton)</td>
<td>E</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Andersen 1986b (79-03) [27]</td>
<td>4</td>
<td>16(18)</td>
<td>mianserine (Hamilton)</td>
<td>non-E</td>
<td>6</td>
<td>40</td>
</tr>
<tr>
<td>Hansen 1984 (79-01)</td>
<td>5</td>
<td>21(22)</td>
<td>nortryptiline (Hamilton)</td>
<td>E and non-E</td>
<td>4#</td>
<td>40</td>
</tr>
<tr>
<td>Johnson 1987 (83-01)</td>
<td>3</td>
<td>23(22)</td>
<td>imipramine (Hamilton)</td>
<td>MDE</td>
<td>4</td>
<td>41</td>
</tr>
<tr>
<td>Ahlfors 1988b (80-09) [28]</td>
<td>9</td>
<td>14(17)</td>
<td>mianserine (MADRS)</td>
<td>non-E</td>
<td>4</td>
<td>42</td>
</tr>
<tr>
<td>Gravem 1987 (80-03) [29]</td>
<td>2</td>
<td>27(24)</td>
<td>amitryptiline (MADRS)</td>
<td>E and non-E</td>
<td>3#</td>
<td>44</td>
</tr>
<tr>
<td>Shaw 1986 (82-07) [30]</td>
<td>1</td>
<td>29(30)</td>
<td>amitryptiline (Hamilton)</td>
<td>MDE</td>
<td>6</td>
<td>46</td>
</tr>
<tr>
<td>Bouchard 1987 (82-06) [31]</td>
<td>6</td>
<td>49(48)</td>
<td>maprotiline (MADRS)</td>
<td>E and non-E</td>
<td>4#</td>
<td>46</td>
</tr>
<tr>
<td>Wilde 1985 (81-02) [32]</td>
<td>8</td>
<td>30(30)</td>
<td>mianserine (MADRS)</td>
<td>E</td>
<td>6</td>
<td>53</td>
</tr>
</tbody>
</table>

*MDE: Major depression episode; E and non-E: Endogenous and non-endogenous depression; # extra weeks with reduced numbers of patients
Illustration 2

Meta-analysis of effects from studies with high and low dose citalopram

[Meta-analysis chart and table with data]
Illustration 3

Regression of dose of citalopram versus effect against comparator drugs
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