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Differences in Adverse Effect Reporting in Placebo Groups in SSRI and Tricyclic Antidepressant Trials

A Systematic Review and Meta-Analysis

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Abstract

Background: Biases in adverse effect reporting in randomized controlled trials (RCTs) [e.g. due to investigator expectations or assessment quality] can be quantified by studying the rates of adverse events reported in the placebo arms of such trials.

Objective: We compared the rates of adverse effects reported in the placebo arms of tricyclic antidepressant (TCA) trials and placebo arms of selective serotonin reuptake inhibitor (SSRI) trials.

Methods: We conducted a literature search for RCTs across PUBMED, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL). Only studies allowing adverse effect analysis were included. Publication year ranged from 1981 to 2007.

Results: Our systematic review and meta-analysis included 143 placebo-controlled RCTs and data from 12 742 patients. Only 21% of studies used structured and systematic adverse effect ascertainment strategies. The way in which trials recorded adverse events influenced the rate of adverse effects substantially. Systematic assessment led to higher rates than less systematic assessment. Far more adverse effects were reported in TCA-placebo groups compared with SSRI-placebo groups, e.g. dry mouth (odds ratio [OR] = 3.5; 95% CI 2.9, 4.2); drowsiness (OR = 2.7; 95% CI 2.2, 3.4); constipation (OR = 2.7; 95% CI 2.1, 3.6); sexual problems (OR =2.3; 95% CI 1.5, 3.5). Regression analyses controlling for various influencing factors confirmed the results.

Conclusion: Adverse effect profiles reported in clinical trials are strongly influenced by expectations from investigators and patients. This difference

cannot be attributed to ascertainment methods. Adverse effect patterns of the drug group are closely related to adverse effects of the placebo group. These results question the validity of the assumption that adverse effects in placebo groups reflect the 'drug-unspecific effects'.

Background

Valid information about adverse effects is crucial for determining the benefit-risk ratio for a given medication or drug class. Some clinical decisions depend at least as much on minimizing adverse effects as on differences in drug efficacy. For example, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) do not differ substantially in efficacy (e.g. Cipriani et al.[1]), but because TCAs are perceived to induce more adverse effects they are prescribed less frequently.[2] Adverse effects also influence patient behaviour in terms of medication adherence and drug discontinuation.[3,4]

Adverse effects are examined in double-blind, randomized controlled trials (RCTs) by comparing the symptoms reported by patients in drug-treated groups with those reported by patients in placebo groups. The expectation is that symptoms found in drug-treated groups result from a combination of specific pharmacological effects as well as non-specific effects that also occur in the placebo groups. These non-specific negative effects of placebos are termed the 'nocebo effect'.[5] The adverse effect profile of the placebo group is assumed to be unrelated to and independent of the active drug to which it is being compared. However, it is possible that the specific drug under study in a double-blind trial could induce patient expectations about adverse effects, and result in such symptoms being reported by the placebo groups.

Although this expectancy effect could be analysed by comparing placebo groups in different drug trials, adverse effect reports are additionally influenced by study quality and ascertainment strategy.[6,7] Therefore, it is important to control for differences in assessment methods when comparing adverse effect profiles across different trials.

We hypothesized that the adverse effects reported with placebos would differ systematically across antidepressant trials. Since TCAs are expected to produce more adverse effects than SSRIs, we postulated that this difference would also be seen in the corresponding placebo groups. Our major interest was in adverse effects that are supposed to be general for the drug group, and less in adverse effects that are assumed to vary within the drug class, because intra-group adverse effects seem to be highly similar.[8] We have previously shown that the adverse effect profile is also influenced by the specific assessment methods used.[6] Therefore, we expected that the use of more specific assessment methods would yield higher rates of adverse effects. However, the difference in adverse effect profiles between TCA placebos and SSRI placebos should be found in studies with systematic assessments, as well as in studies with less systematic adverse effect assessments. To test our hypotheses, we conducted a systematic review of published RCTs of antidepressants that reported adverse effect rates for placebo groups.

Methods

Search Procedure

We conducted a literature search for RCTs across PUBMED, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) from the first available year to March 2007, resulting in the first included study originating from 1981. All studies that included one of the following terms in the title were considered: 'sertraline', 'fluoxetine', 'citalopram', 'paroxetine' 'escitalopram', 'fluvoxamine', 'imipramine', 'amitriptyline', 'doxepin', 'clomipramine', 'trimipramine', 'amitriptylinoxide', 'desipramine', 'dosulepin' and 'nortriptyline'. We also searched published meta-analyses on antidepressants to identify additional studies that were not included in the databases mentioned above.

Studies were selected for inclusion according to the following criteria: (i) only randomized, placebo-controlled clinical trials of TCAs or SSRIs, or secondary analysis of relevant RCTs were included (in order to detect drug-associated expectancy effects in the placebo group, studies comparing TCAs and SSRIs in the same trial were excluded as it was unclear which adverse effect pattern would be expected in these trials); (ii) only studies addressing the treatment of anxiety or depressive disorders were included; (iii) studies had to report base rates of adverse effects in the placebo groups; and (iv) publication languages included English, French and German. Figure 1 represents a flow chart with detailed information on our study selection according to the Quality of Reporting of Meta-analyses (QUORUM) statement.[9]

Data Extraction and Quality Assessment

Each study was coded using a structured coding scheme[1], including information on general characteristics of the studies, methods, dropout rates, participant diagnoses, drug treatment and methodological quality. The quality of the studies was rated according to the Jadad score[10] using items such as 'adequately randomized', 'adequately double blinded' and 'report of dropouts' as the criteria. While the Jadad score ranges from 0–5, we added further study quality criteria (e.g. description of diagnoses and detailed description of randomization procedure) to increase the range of the quality score to 0–9. The assessment of adverse effects was categorized as 'unsystematic, spontaneous reports' versus 'structured recording' (e.g. using a checklist or self-rating scale). Adverse effects were grouped into 26 frequently reported symptoms and a residual category. The adverse effect categories were defined after analysing the symptoms reported in 20 randomly chosen studies (ten SSRI studies and ten TCA studies). To assess the quality of the coding process, a random selection of 38 studies was re-coded by a second rater. Mean inter-rater reliability of the two independent raters was kappa coefficient = 0.96 for general features of the study, quality items and sample characteristics. The mean reliability coefficient for adverse effects was 0.99, indicating that the coding process was sufficiently reliable.

Data Integration

Because we focussed on adverse effects and not on mean effect sizes as in usual meta-analysis, the procedure had to be adjusted. Adverse effects were categorized into 18 symptom groups, and symptom frequency was coded. Because most variables were binary, as the first step we computed percent scores (and 95% confidence intervals [CIs] where indicated), representing the number of patients with each recorded symptom in the placebo group. The percentages of patients reporting adverse effects have been weighted according to the sample size of each trial. We used a linear weighting model according to sample size, which seems adequate if no extreme outliers of sample size occur (mean n of placebo group = 89; SD = 81; 66% of studies report placebo groups with sample sizes below 95; continuous slope with no obvious outliers; maximum n = 445). We analysed differences in weighted percentages with chi-square scores. As the second step, ORs and corresponding CIs were computed for unstructured assessed adverse effects compared with standardized assessed adverse effects, and for TCA placebo adverse effects compared with SSRI placebo adverse effects.

Co-Variate Analysis

The influence of several categorical co-variates (i.e. assessment strategy for adverse effects,[6] age,[11] diagnosis and sex[12] of patients) and one continuous co-variate (publication year[13]) was tested by weighted percentage scores and risk ratios ('moderator analyses'). This procedure is based on a model of random effects. For the eight adverse effects reported in most studies (>50 studies), we computed regression analyses, including all relevant variables, to identify whether

1 The full version of the coding scheme and the quality rating are provided as online Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A17.

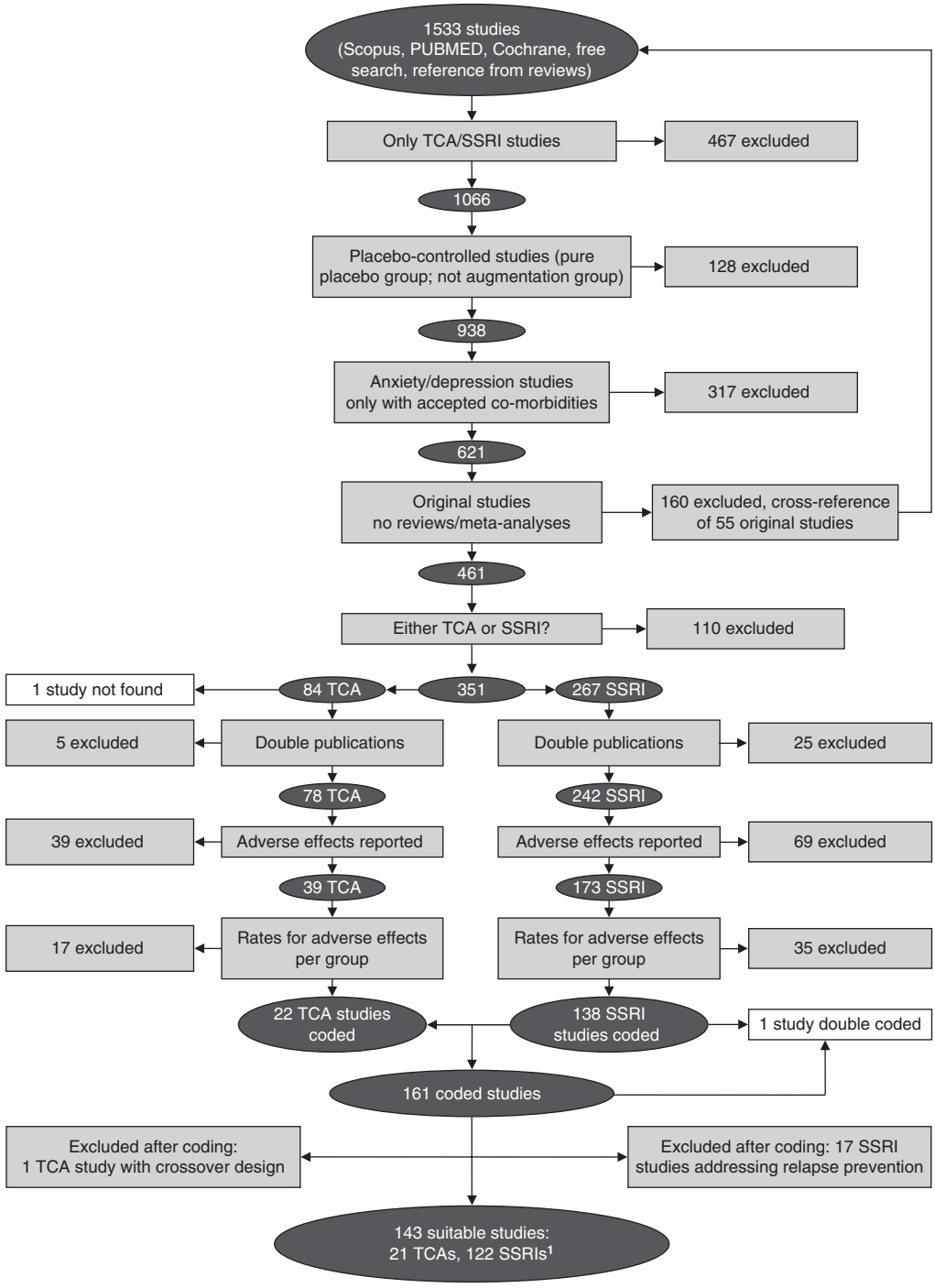

Fig. 1. Flow chart of our study selection according to the Quality of Reporting of Meta-analyses (QUORUM) statement.[9] **1** One study reported two placebo groups therefore it was included twice. **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant.

medication in the drug group still influences adverse effect patterns of placebo groups even after controlling for ascertainment strategy, diagnosis differences, publication year, age and sex differences.

Results

A total of 143 studies[14-155] [2] including 12 742 patients (11 719 in SSRI placebo groups, 1023 in TCA placebo groups) were analysed (see figure 1). Mean patient age was 39.8 years and 55.2% of patients were female. Many studies did not report adverse effects or specific adverse effect rates for the placebo groups. Therefore, 56 of 78 TCA trials (72%) and 104 of 242 SSRI trials (43%) could not be entered in our analysis. The final sample consisted of 122 SSRI studies and 21 TCA studies. Included SSRI studies investigated the following drugs: citalopram (14), escitalopram (12), fluoxetine (30), fluvoxamine (14), paroxetine (30) and sertraline (31), while the TCA studies investigated clomipramine (10), imipramine (4), nortriptyline (2), desipramine (2), doxepin (2), lofepramine (2), and amitriptyline, trimipramine and dosulepin (1).

TCA studies and SSRI studies were not significantly different in terms of patient age, but TCA studies included slightly more women than SSRI studies (58.4% vs 54.9%; $p < 0.002$). Jadad study quality scores were comparable between groups, with 90% of TCA studies and 96% of SSRI studies yielding Jadad scores ≥3 ($p > 0.20$). For 46% of the studies, the assessment method of adverse effects was either 'spontaneous comments' or not reported; 21% of studies used a structured checklist or rating scale, while 33% of studies reported some systematic and regular assessment but no structured method.

Diagnoses

More studies targeted anxiety disorders (number of studies [k] = 80; 56%; total sample size 7371) than depressive disorders (k = 63; 44%; total sample size 5371). Although somewhat more SSRI studies are reported for anxiety disorders than for depression, the relationship of SSRI studies and TCA studies did not differ significantly between diagnostic groups; 57% of all SSRI studies and 53% of all TCA studies targeted anxiety disorders ($p > 0.50$). Reported medical co-morbidity rates were low (12% in SSRI studies and 14% in TCA studies; $p > 0.50$). Of the 63 depression studies, most studies included mainly patients with major depression {DSM-IV/depressive episodes (International Classification of Disease – 10th Revision [ICD 10])} [53 studies], while anxiety studies (k = 80) addressed patients with panic disorder (k = 12), social phobia (k = 16), obsessive-compulsive disorder (k = 28), post-traumatic stress disorder (k = 9) and 15 others.

Discontinuation Rates

Discontinuation rates were nearly identical between the placebo groups and the corresponding drug groups (24.7%; 95% CI 22.5, 27.0 vs 24.8%; 95% CI 22.5, 27.0), and did not differ significantly between TCA placebos and SSRI placebos (one-way ANOVA F-score = 1.7; not significant).

Quality of Study; Quality of Adverse Effect Assessment

The quality of the ascertainment method strongly determined the base rate of reported symptoms (table I). We compared systematic versus unsystematic assessment methods for all adverse effects reported in at least five studies. 14 of 17 symptoms showed significant differences between systematic and unsystematic assessments, with higher rates associated with more systematic assessments (e.g. vision/accommodation problems 13.5% vs 1.9%; tremor 8.0% vs 2.1%; dizziness 15.1% vs 7%; $p < 0.001$ for all). These differences are extremely robust because they are based on the comparison of 46 studies on average. The mean OR is 2.6 (mean CI 2.1, 3.3), which means that the probability of reporting adverse effects is more than twice as high when structured assessment methods are used.

2 Sheikh et al.[121] reported two placebo groups, therefore this study was included twice.

Table I. Different adverse effect profiles in placebo groups depending on ascertainment strategy (only symptoms reported in at least five studies included)

Symptoms	Unsystematic assessment[a]		Systematic assessment[b]		k_{total}	OR (95% CI)[c]
	N (k)	n (%)	N (k)	n (%)		
Vision/accommodation problems	591 (5)	11 (1.9)	192 (8)	26 (13.5)	13	**8.3 (4.0, 17.1)**
Fatigue	2303 (19)	108 (4.7)	265 (8)	47 (17.7)	27	**4.4 (3.0, 6.3)**
Tremor	2622 (22)	55 (2.1)	324 (12)	26 (8.0)	34	**4.1 (2.5, 6.6)**
Increased appetite/weight gain	420 (6)	16 (3.8)	188 (5)	19 (10.1)	11	**2.8 (1.4, 5.6)**
Weight loss	2376 (25)	61 (2.6)	306 (10)	20 (6.5)	35	**2.7 (1.6, 4.5)**
Dizziness	4044 (34)	284 (7.0)	856 (18)	129 (15.1)	52	**2.4 (1.9, 2.9)**
Drowsiness	5668 (51)	399 (7.0)	608 (14)	90 (14.8)	65	**2.3 (1.8, 2.9)**
Constipation	2331 (20)	111 (4.8)	432 (14)	44 (10.2)	34	**2.3 (1.6, 3.3)**
Sexual problems	5106 (42)	112 (2.2)	741 (10)	33 (4.5)	52	**2.1 (1.4, 3.1)**
Sweating	2981 (25)	180 (6.0)	740 (12)	87 (11.8)	37	**2.1 (1.6, 2.7)**
Nervousness	2608 (28)	178 (6.8)	296 (11)	37 (12.5)	39	**2.0 (1.3, 2.8)**
Insomnia	6755 (56)	739 (10.9)	796 (16)	124 (15.6)	72	**1.5 (1.2, 1.9)**
Diarrhoea	5249 (43)	413 (7.9)	685 (9)	76 (11.1)	52	**1.5 (1.1, 1.9)**
Abdominal pain	2483 (25)	210 (8.5)	378 (11)	46 (12.2)	36	**1.5 (1.1, 2.1)**
Dry mouth	4200 (43)	333 (7.9)	812 (19)	80 (9.9)	62	1.3 (1.0, 1.6)
Nausea	8168 (75)	884 (10.8)	864 (19)	112 (13.0)	94	1.2 (1.0, 1.5)
Headache	4700 (49)	1034 (22.0)	574 (14)	121 (21.1)	63	1.0 (0.8, 1.2)

a Spontaneous and 'regular' reports.

b Systematic assessment: checklists.

c Adverse effect risk in systematic vs unsystematic assessed placebo groups; bold denotes $p < 0.05$.

k = number of placebo groups reporting the symptom; **N** = total sample size in the placebo group; **n** = number of patients in the placebo group reporting the symptom; **OR** = odds ratio.

Do Adverse Effects in Placebo Groups Reflect Adverse Effect Patterns in Drug Groups?

One pivotal assumption of our approach is the hypothesis that adverse effect rates in placebo groups reflect adverse effect patterns in drug groups. To confirm this assumption, we correlated symptom rates in placebo groups with symptom rates in drug groups. We selected those eight symptoms reported in at least 50 studies and found significant Pearson's r correlation for all of them. Only a modest effect was found for sexual dysfunctions ($r = 0.27$; $p < 0.05$), while three other symptoms showed correlations above $r > 0.70$ (diarrhoea, drowsiness, dry mouth; $p < 0.001$ for all), and three symptoms showed correlations between 0.60 and 0.65 (insomnia, headache, dizziness; $p < 0.001$ for all). Therefore, reported drug adverse effects share major parts of the variance with reported placebo adverse effect patterns.

Adverse Effects with Tricyclic Antidepressant Placebos versus Selective Serotonin Reuptake Inhibitor Placebos

To analyse robust effects, we only included symptoms reported in at least five studies per drug group (see table II). TCA placebos were associated with higher symptom rates than SSRI placebos for 10 of 18 symptoms (e.g. dry mouth 19.2% vs 6.4%; vision/accommodation problems 6.9% vs 1.2%; fatigue 17.3 vs 5.5%; constipation 10.7% vs 4.2%; $p < 0.001$ for all), while two symptoms were reported more frequently in SSRI placebo groups (sedation, increased appetite). The latter two resulted from comparisons of only a few studies (six TCA studies and six SSRI studies were compared); therefore, we will not interpret them in detail. Some of the symptoms reported more frequently in TCA studies result from very large total samples

(e.g. dry mouth: 79 studies including more than 6400 patients) and can be considered as very robust.

To check whether the symptom differences between groups are due to low ascertainment quality, we reanalysed all studies using only systematic ascertainment strategies. For all symptoms showing significant differences between TCA- and SSRI-placebo groups when all studies were included (table II), this difference was confirmed when only studies with systematic ascertainment strategies were included, except for headache and sedation. Some differences were even more pronounced when comparing only studies with systematic adverse effect assessment (OR for TCA placebo groups compared with SSRI placebo groups: dry mouth OR = 5.5; fatigue OR = 7.9; dizziness OR = 2.3; $p < 0.001$ for all).

Although these effects of the drug category on placebo symptom profiles are impressive, it is still unclear whether they are due to some other factors that are not balanced between the groups. Therefore, we computed regression analyses, again with those eight symptoms reported in at least 50 studies. As the first block of variables, we entered age, publication year, sex and systematic assessment in a stepwise approach. As the second block of variables, we entered the variables diagnosis and drug group. For four of the eight symptoms, this regression analysis yielded a significant model ($F_{min} = 8.31$; $p < 0.001$). Except for headache, drug group (SSRI vs TCA) was confirmed as a significant predictor of adverse effects in the placebo groups (dry mouth beta coefficient [β] = 0.61, $p < 0.001$; drowsiness β = 0.40, $p < 0.001$; dizziness β = 0.24, $p < 0.05$) even after controlling for all other variables. With regard to the co-variates, 'systematic assessment' was a significant moderator for the symptoms 'drowsiness' (β = 0.31; $p < 0.003$) and 'dizziness' (β = 0.33; $p < 0.008$), while all other co-variates did not contribute significantly to the second-order models.

Table II. Comparing adverse effects in selective serotonin reuptake inhibitor (SSRI) placebo groups and tricyclic antidepressant (TCA) placebo groups (only symptoms that were reported in at least five studies)

Symptom	TCA studies		SSRI studies		k_{total}	OR (95% CI)[a]
	N (k)	n (%)	N (k)	n (%)		
Vision/accomodation problems	683 (11)	47 (6.9)	504 (7)	6 (1.2)	18	**6.1 (2.6, 14.5)**
Fatigue	521 (7)	90 (17.3)	3307 (31)	182 (5.5)	38	**3.6 (2.7, 4.7)**
Tremor	858 (15)	31 (3.6)	2947 (31)	63 (2.1)	46	**1.7 (1.1, 2.7)**
Increased appetite/weight gain	324 (6)	11 (3.4)	298 (6)	23 (7.7)	12	**0.42 (0.20, 0.88)**
Weight loss	394 (5)	7 (1.8)	3123 (38)	90 (2.9)	43	0.6 (0.3, 1.3)
Dizziness	859 (15)	118 (13.8)	5370 (52)	413 (7.7)	67	**1.9 (1.55, 2.4)**
Drowsiness	847 (13)	142 (16.8)	7247 (66)	496 (6.8)	79	**2.7 (2.2, 3.4)**
Constipation	945 (17)	101 (10.7)	2767 (30)	116 (4.2)	47	**2.7 (2.1, 3.6)**
Sexual problems	545 (8)	26 (4.8)	7054 (58)	151 (2.1)	66	**2.3 (1.5, 3.5)**
Sweating	553 (9)	36 (6.5)	4358 (38)	157 (3.6)	47	**1.9 (1.3, 2.7)**
Nervousness	404 (6)	26 (6.4)	3000 (38)	207 (6.9)	44	0.9 (0.6, 1.4)
Insomnia	800 (12)	106 (13.3)	8641 (80)	955 (11.1)	92	1.2 (1.0, 1.5)
Abdominal pain	514 (6)	43 (8.4)	3311 (41)	298 (9.0)	47	0.9 (0.7, 1.3)
Dry mouth	993 (20)	191 (19.2)	5422 (59)	346 (6.4)	79	**3.5 (2.9, 4.2)**
Nausea	817 (13)	98 (12.0)	10 910 (111)	1148 (10.5)	124	1.2 (0.93, 1.44)
Headache	849 (14)	233 (27.4)	6271 (70)	1250 (19.9)	84	**1.5 (1.3, 1.8)**
Urinary retention	389 (6)	16 (4.1)	271 (6)	6 (2.2)	12	1.9 (0.7, 4.9)
Sedation	148 (6)	7 (4.7)	297 (6)	38 (12.8)	12	**0.34 (0.15, 0.78)**

a Adverse effect risk in TCA placebos in relation to SSRI placebos; significant differences are denoted in bold.

k = number of placebo groups reporting the symptom; **N** = total sample size in placebo group; **n** = number of patients in the placebo group reporting the symptom; **OR** = odds ratio.

Additional Analyses

We also wanted to analyse whether publication year had a significant impact on adverse effect rates. Therefore, we computed correlations of the frequency of the eight most frequently reported adverse effect symptoms (e.g. dry mouth, nausea) with publication year; all correlation coefficients were below $r = 0.23$, indicating only minor influences of publication year. For exploratory reasons, we also compared depression trials ($k = 63$) with anxiety trials ($k = 80$). Several comparisons revealed more adverse effects in anxiety patients compared with depressive patients (e.g. nausea 11.7% vs 9.1%; drowsiness 8.6% vs 6.8%; sexual problems 2.6 vs 1.5%; $p < 0.006$ for all). However, because of further differences between these samples (e.g. age, sex, co-morbidity patterns) these results will not be further interpreted.

Discussion

TCAs are widely believed to induce more adverse effects than SSRIs.[156,157] After a comprehensive review of published randomized controlled trials for both drug classes, we found that this difference was not only observed in the drug groups of each respective drug class, but also in the placebo arms for most symptoms. There are a number of issues that need to be considered in interpreting these findings. Before discussing expectations as a major source of this effect, we will discuss whether methodological differences can account for these findings. Afterwards, we will discuss how investigator expectations could have influenced the study results. A third possibility would be that patient expectations (which are partly determined by the investigators and other sources of information) led to different symptom reports.

Our results confirm that structured assessment approaches reveal much higher rates of symptoms than do unstructured approaches. There is also clear evidence that more structured approaches for ascertainment lead to more reliable results.[158] However, the majority of antidepressant trials we reviewed either did not report an adverse effect ascertainment strategy or did not use a structured assessment (e.g. checklist or rating scale). This indicates a need to improve the quality of adverse effect assessment procedures and reporting. Again, it is confirmed that results of the placebo groups are intrinsically tied to the trial methodology and results.[159] It has recently been shown that physicians tend to deny patient reports of adverse drug effects,[160] and this can be controlled by more standardized ways of assessing adverse effects. However, these methodological issues are unlikely to explain the differences between TCA and SSRI placebos since these differences persisted when we restricted the analysis to studies that used structured assessment strategies.

The Rosenthal[161] effect has shown that investigator expectancy can substantially affect the outcome of experimental investigations. It is likely that investigators expected substantial differences between adverse effect profiles of SSRIs and TCAs, an expectation that would show greater effects with less stringent or less reliable assessment instruments. In other studies using standardized scales to assess adverse effects and comparing TCAs and SSRIs directly, no adverse effect difference was found for the total score or for any of the subscales;[162] however, substantial differences were reported for a comparable sample when less structured methods were used.[11] These findings provide additional evidence in favour of using rigorous adverse effect ascertainment methods in clinical trials of medications.[6] Even for differences in tolerability of drugs that are supposed to be well proven (such as SSRIs vs TCAs), our results question the robustness of these assumptions.

Patient expectancy is another potential source of adverse effects associated with placebos. When participants in clinical studies are informed in detail about the possible adverse effects of a study drug, they can expect to experience them; this expectancy may differ between TCA- and SSRI-placebo groups. SSRIs are typically expected to have a stronger activation effect, whereas TCAs frequently induce dry mouth, drowsiness and other symptoms. In general, symptoms such as headache (15%), joint pain (17%) and dizziness (5%) are frequently reported by patients receiving placebo treatment.[163] Using experimental approaches, it has been shown that a variety of symptoms can be provoked by inducing specific expectations,

including motion-induced nausea,[164] allergic drug reactions[12] and tension.[165] Link et al.[166] found that patients who believed they had received a herbal drug reported more symptoms than patients who were under the assumption that they had received a placebo, although both groups received an inert substance. For visceral pain, it was shown that the expected pain level was the major determinant of reported pain intensity, while the effect of using placebos or lidocaine (lignocaine) itself contributed only slightly to the variance of the pain perception.[167] Thus, there is good evidence that patient expectation can modify base rates of reported adverse effects.

If expectations can influence symptom reports, this should be associated with neurophysiological processes in the sensory-perceptual pathways. Lorenz et al.[168] demonstrated that the expectation of pain was associated with nearly the same electromagnetic and electrophysiological brain reactions as a real pain stimulus. Further biological pathways explaining the reactions to placebos (e.g. the opioid system) have been identified.[169-172] Moreover, the negative expectation of pain triggers the activation of cholecystokinin, which, in turn, facilitates pain transmission.[173]

Although expectation can induce new physical symptoms, some participants in clinical trial placebo groups may not experience new symptoms, but may instead attribute pre-existing symptoms to the drug being studied. Complaints of headache, back pain and abdominal discomfort are extremely common in the general population, with base rates of severe conditions reaching up to 30% and base rates of minor physical symptoms reaching up to over 80%.[174,175] These symptoms could thus easily be misclassified as adverse effects of the drug. Even in our study, it cannot be determined whether the group differences are due to differences in new symptoms or to differences in attributing existing symptoms. Therefore, drug trials need to consider the base rates of pre-existing general complaints more rigorously in order to distinguish drug-associated adverse effects from the general base rates of symptoms.[6]

The nocebo effect can be explained by other psychological processes as well.[5,176] Anxiety and optimism can modulate the placebo response,[177,178] although we found the same pattern of results when only depressive patients were compared.

The prior experiences of patients can also be important because many participants in clinical trials have used antidepressants before entering the studies. Prior experience of symptom provocation can lead to sensitization processes that increase both placebo and nocebo effects.[179,180] Therefore, classical conditioning has been suggested as one way to develop nocebo symptoms.[5,181] If patients experienced adverse effects during former treatments with antidepressants, it is likely that they will develop similar 'adverse effects' even after receiving placebos. While we could not analyse how many patients were previously exposed to antidepressants and experienced adverse effects, we expect that these rates did not vary systematically between SSRI- and TCA-placebo groups.

Limitations

Meta-analyses and other systematic overviews are prone to selection biases, and only a limited number of mediating factors could be analysed. We controlled for systematic influences of age, sex and diagnoses; we could not show substantial biases due to publication year.[13] Although our analyses of confounding factors may not have been able to reveal all details of their influence, the differences between the rates of adverse effects (e.g. depending on ascertainment strategy or drug group) are much higher than what is known about the influence of any of the other confounding factors. Publication bias can also lead to serious misinterpretation of findings, as recently shown for the efficacy of some antidepressants.[182,183] However, the reported effects are based on large samples and can be considered to be very robust, and 'fail-to-safe-k' (number of postulated unpublished studies not showing a difference between TCA placebo groups and SSRI placebo groups) can be estimated to be much higher than the number of published trials; therefore, publication bias is very unlikely to explain the results. Furthermore, as we wanted to analyse possible expectancy effects, we did not include any trial designs comparing TCAs and SSRIs

directly, which could have led to further selection biases. A stronger limitation of our analysis comes from the differing and frequently unstructured methods of assessing adverse effects among the studies. The problem of missing information on adverse effects in clinical trials was confirmed in other analyses. Of 37 trials comparing SSRIs and TCAs in older patients, 26 studies (70%) failed to provide sufficient adverse effect data.[157] Many trials reported relatively few symptoms and it remains unclear how many symptoms were assessed in total. Focusing on studies with structured assessment strategies substantially reduced the number of included studies, thereby increasing the risk of selection bias. However, the differences between TCA placebo groups and SSRI placebo groups are found both for structured and unstructured assessment strategies. Finally, prior exposure and experience of adverse effects when taking drugs is a substantial factor that was not controlled for in our analyses, although it influences expectation and conditioning of symptoms.

Symptom expectations of patients were likely to have been influenced by the consent forms used in the specific trials. Adverse effects mentioned in informed consents might not only increase expectation effects but might also facilitate the perception and reporting of these symptoms. This 'biasing of symptoms' can depend on several features, e.g. number of symptoms on the list or oral versus written information. The degree to which specific adverse effect symptoms were provided to patients in the informed consent forms probably varied greatly among the studies and may have contributed to the results. Moreover, this symptom biasing can interact with the ascertainment method. A structured approach of adverse effect assessment is based on 'recognition memory' and might not only reduce the risk of forgetting but also sensitize and amplify a symptom perception and memory process that started with the informed consent. Unstructured ascertainments are based on 'recall memory', which is more prone to forgetting than recognition memory. Data from clinical trials with triptans found that 7.5% of participating patients reported no adverse effects at all in unprompted questionnaires but rated some adverse effects even as 'severe' in the prompted questionnaire.[7] Subsequent studies should attempt to analyse the effects of different informed consent forms and their interaction with ascertainment strategies more systematically.

Conclusion

Our results question the basic assumption of clinical trials, namely that all unspecific effects are reflected in the placebo group, while the drug group shows the additive effect of the chemical drug action. Clearly, the adverse effect patterns of placebos reflect, in part, the adverse effects expected for the drug, which complicates the detection of drug-induced adverse effects. To reduce possible investigator effects, it would be helpful for the rater to be blind to the expected adverse effects of the drug being tested. Considering expectancy effects of patients, the balance between ethical considerations (the necessity to inform patients about expected adverse effects) and scientific needs (to reduce any expectancy effects) presents a difficult conflict. Perhaps most importantly, our results document that adverse effect profiles between different drugs (e.g. SSRIs, TCAs) are prone to systematic expectation influences. Although the pooling of studies is the typical way to analyse general (side) effects,[184,185] pooling can be problematic. Pooling studies based on placebo groups with one specific expectation of adverse effect profiles, and comparing these results with pooled other studies based on placebo groups with other expectations, can lead to false conclusions about typical adverse effect profiles of drugs. In pooled analyses, it should be shown that the corresponding placebo groups did not differ in the same way as the drug groups. The interpretation of drug trial results depends essentially on results of placebo groups; therefore, placebo groups must be designed with care[159] and adverse effect assessment methods need substantial improvements.

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