Pain Relief in Depressive Disorders

A Meta-Analysis of the Effects of Antidepressants

Stefan Gebhardt, MD, Monika Heinzel-Gutenbrunner, PhD,† and Udo König, MSc†*

Background: Pain is a common symptom in patients with depressive disorders, which, if present, worsens the prognosis. However, there is little empirical knowledge of the therapeutic effects of antidepressants on painful physical symptoms of patients with depressive disorders. Furthermore, tricyclic/tetracyclic antidepressants (TCAs) have not yet been included in existing meta-analyses.

Methods: A broad, systematic search of PubMed literature on antidepressant drug treatment of patients with depressive disorders with comorbid pain symptoms was carried out. A random-effects meta-analysis has been performed among 3 different groups of drugs for the 2 end points: pain and depression.

Results: Fourteen placebo-controlled studies with selective serotonin-noradrenaline reuptake inhibitors (SSNRIs) could be included, with 3 of them also investigating selective serotonin reuptake inhibitors (SSRIs). Three further placebo-controlled SSRI studies were identified, but only 2 placebo-controlled TCA studies.

Both SSNRIs and SSRIs, but not TCAs, were significantly superior to placebo as regards their analgesic effects. However, all effects were small. For SSNRIs, there was a strong positive correlation between their effectiveness for pain relief and their positive effect on the mood of the patients.

Discussion: The analgesic effects of SSNRIs and SSRIs in patients with primary depressive disorders can be interpreted as largely equivalent. Because of a lack of placebo-controlled TCA studies, the results for TCAs would be comparable only to those of SSRIs and SSNRIs, if non–placebo-controlled TCA studies were included. The positive correlation found indicates a close relationship of pain relief and antidepressant treatment effects. These results refer merely to patients with primary depressive disorders, not to patients with primary pain disorders. Further studies comparing the effects of different types of antidepressant drugs on pain in depressive patients are warranted.

Key Words: antidepressants, depression, meta-analysis, pain, treatment, tricyclic

(*J Clin Psychopharmacol* 2016;36: 658–668)

Pain is a common symptom in patients with depressive disorders and plays a crucial role not only in psychiatry and psychosomatic medicine, but also in nearly all areas of public health. There is a great need for evaluated therapeutic strategies, which, however, are still sparse. Therefore, the current meta-analysis focuses on the impact of various antidepressant drugs (ADs) on pain as a symptom in depressive disorders.

Epidemiological data reflect the immense clinical impact of the comorbidity of depression and pain on public health worldwide, not to speak of the likelihood of a substantial diagnosis-treatment gap. Five percent to 13% of the general population has a depressive disorder; a third hereof can be classified as chronic.[1–3] Pain occurs in 43% to 75% of patients with depressive disorders,[3–6] and the association between depression and painful physical symptoms is clearly recognized.[3,7] Depressed patients presenting with pain as a symptom have a worse prognosis.[8,9]

The comorbidity of a depressed mood and physical pain is currently explained by several theories. First, the comorbidity can represent 2 sides of the same coin, based on neurobiology,[10,11] caused by a dichotomization of physical (pain) and psychological (depression) stress. Second, a bidirectional, dynamic relationship is assumed, whereby a disequilibrium in one functional system (eg, depressive mood) tends to cause nonlinear changes in other functional systems (eg, stress with coping, psychosocial relationships, pain transmission system).[12,13] Third, the inflammatory hypothesis focuses on chronic inflammation with common neuroimmune mechanisms underlying both depression and pain.[14] Finally, a couple of studies have shown associations among stress; altered hormone responses (corticotrophin-releasing hormone, cortisol); alterations of neurobiological brain regions, involved in the regulation of both affect and pain; and the catecholamine system.[15–19] The descending inhibitory pathways have been discussed as the preferred pathophysiological model.[18–25]

Antidepressants show alleviating effects both on symptoms of pain and depression. Antidepressants modulate not only neurotransmitter systems, but also opioid receptors, as well as endocrine, immune, and signaling-related mediators and neuroplasticity.[26–32] They are supposed to equalize an altered function of the hypothalamic-pituitary-adrenal axis, of insufficiently active descending pain-inhibiting tracts at the level of the dorsal horn neurons, and of higher areas such as the rostral-ventromedial medulla.[28–32] However, the specific effects of ADs on pain modulation, especially in cortical and subcortical areas, are not entirely understood.

Although there are several studies on the efficacy of ADs as pain relief for patients with primary pain diseases (eg, tricyclic ADs on neuropathic pain[33]), studies about the analgesic effects of ADs in patients with depressive disorders are comparably rare. Furthermore, tricyclic/tetracyclic ADs (TCAs) have not yet been included in existing meta-analyses of the treatment of pain in depressive disorders.[34–36]

Despite this presently poor empirical research base concerning therapeutic options for pain relief in patients with depressive disorders, clinicians are obliged to choose the right medication. Based only on clinical estimations, tricyclic ADs are often used. In recent years, duloxetine has become more and more popular. Interestingly, no studies exist so far comparing the therapeutic effects of duloxetine to tricyclic ADs in patients with depressive disorders, suffering also from pain.

The aim of this meta-analysis is therefore to test the following hypotheses that (*a*) ADs of different classes vary in their effects on painful symptoms in depressive disorders, (*b*) ADs have a noticeable effect on the pain symptoms in depressive disorders, and that (*c*) there is a positive correlation between the therapeutic effects on symptoms of depression and on those of pain.

From the Departments of *Psychiatry and Psychotherapy and †Child and Adolescent Psychiatry, Philipps-University of Marburg, Marburg, Germany.
Received December 29, 2015; accepted after revision September 7, 2016.
Reprints: Stefan Gebhardt, MD, Department of Psychiatry and Psychotherapy, University of Marburg, Rudolf-Bultmann-Str. 8, D-35039 Marburg, Germany (e-mail: Stefan.Gebhardt@uni-marburg.de).
Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000000604

MATERIALS AND METHODS

Literature Search and Study Selection

A broad systematic PubMed literature research was conducted on placebo-controlled studies that were concluded before 2015. This investigated selective serotonin-noradrenaline reuptake inhibitors (SSNRIs), selective serotonin reuptake inhibitors (SSRIs), and TCAs in adult patients with a primary depressive disorder and comorbid pain symptoms. The search strategy combined the following keywords: "depression," "depressive," "pain," "antidepressant(s)," and all names of ADs. An adjustment of reports from the database and from additional sources took place: we hand-searched reference lists of pertinent review articles and contacted authors and pharmaceutical enterprises to clarify reports and identify additional unpublished data.

Retrieved records were initially screened by title plus abstract. Abstracts of studies were considered potentially eligible for inclusion and retrieved in full text if they reported (*a*) an empirical investigation (ie, excluding review, meta-analysis, and single-case studies), (*b*) in populations with depressive disorders as primary disorder (excluding animal or cell studies or only control subjects), and (*c*) the presence of pain recordings and ideally also of depression scores under AD medication.

The entire texts were then screened to see if they met the inclusion criteria. Study inclusion criteria comprised the following: (*a*) studies on adult patients suffering from an unipolar depressive disorder as primary disorder (not as a secondary depression following a primary pain history); (*b*) objective measures on pain reduction and, ideally, also depression reduction; (*c*) sufficient quantitative data reported in the studies to estimate an effect size; (*d*) treatment duration of at least 6 weeks; (*e*) sufficient empirical study design and statistical methodology; (*f*) existence of a placebo control group; (*g*) publication in a peer-reviewed journal in English, German, or French.

One of the biggest challenges in this huge literature search was that research studies focused on several different ways of comorbidity of pain and depression, in the context of the following disorders: neuropathic pain, functional pain syndromes, autonomic somatoform disorder, persistent somatoform pain disorder, somatization disorder, posttraumatic stress disorder, conversion disorders, fibromyalgia syndrome, depressive disorders, and others. In order to avoid selection bias effects, we focused on the assessment of pain as a symptom in depressive disorders, which is characterized by a simultaneous or subsequent development with or after the onset of depression. We emphasize that data on primary pain disorders (eg, chronic pain symptoms) with subsequent depression or depressive symptoms, respectively, have not been included in the current study.

The quality of the studies was independently assessed by an expert rating by 2 authors (S.G., M.H.-G.) according to inclusion criteria (see above), respectively. In the case of disagreements, the third author (U.K.) was involved in order to provide another independent estimation, resulting in a resolution by discussion and consensus on the basis of the search guidelines and inclusion criteria.

Because the purpose of this review was to give a broad and independent overview on current options for the AD treatment of pain symptoms in depressive disorders, we also included studies on TCAs that have been ignored by current meta-analyses, as long as they met the previously mentioned inclusion criteria. To exclude publication biases, full texts that reported on completely overlapping study samples or that did not dispose of confounding variables or other modifiers were excluded from review.

Statistical Analysis

For each study, the authors extracted the following study details: participant characteristics, study design, dropout rate, and pain/depression measures. A random-effects meta-analysis (RE model) has been performed for the 2 end points, pain and depression, and the substance groups. The effect sizes concerning improvement in pain and depression were calculated by means of the R package "compute.es" and were expressed in Cohen *d*.[37] Meta-analyses were conducted with the R package "metafor."[38] Results on pain effects are expressed as forest plots with combined effect sizes. We assessed statistical heterogeneity in effects between studies by calculating Cochran *Q*. We used the I^2 statistic (the proportion of variation in study estimates attributable to heterogeneity) to estimate the magnitude of heterogeneity. Funnel plots were added to assess potential publication bias, but given the small numbers of studies in our meta-analyses, these tests have a low sensitivity to detect publication bias. Finally, the correlation between the effect sizes of both pain and depression pairs of values (for each study) was assessed.

RESULTS

Study Selection

The screening of abstracts and titles in PubMed according to the previously mentioned procedure yielded 59 studies (see search flowchart in Fig. 1). After reviewing the full texts, 40 studies were excluded because they did not meet the inclusion criteria.

Thus, a total of 19 studies were retained for the meta-analysis. Table S1 (see Supplemental Digital Content 1, http://links.lww.com/JCP/A390) summarizes the study characteristics, including study design, medication and dosage, treatment duration, participant ages/gender, pain/depression measures, and results concerning outcome data on depression, pain, and relations of both.

Characteristics of the Selected Studies

Fourteen placebo-controlled SSNRI studies could be included, with 3 of them also investigating SSRIs. Three further placebo-controlled SSRI studies were identified, but only 2 placebo-controlled TCA studies. These studies comprised a total of 6135 participants, of whom 2713 participants received placebo, 2450 duloxetine, 314 paroxetine, 272 venlafaxine, 261 fluoxetine, 75 escitalopram, 30 doxepin, and 20 participants received mianserin. Sufficient depression outcome scores were available in all studies except for 1 SSRI study.[55]

All SSNRI studies were done on duloxetine (dosages between 60 and 120 mg/d) except for 2 studies on venlafaxine (50 mg/d[51]; 177 mg/d[44]). The studies assessing SSRI effects were done on paroxetine (4 studies, all with a daily dosage of 20 mg[41,42,45,54]), fluoxetine 20 mg/d,[53] and escitalopram 10 mg/d.[55] The 2 placebo-controlled TCA studies were done on doxepin (200 mg/d[61]) and mianserin (90 mg/d[63]).

The instruments mainly used to evaluate mood were Hamilton Rating Scale for Depression and Montgomery-Åsberg Depression Scale for depression and visual analog scale and Brief Pain Inventory for pain (see Table S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A390). Four studies did not provide exact data on depression outcome scores and were not included in the meta-analyses of effects on depression.[55,56,60,64]

The mean age of the participants ranged from 38 to 73 years, and the treatment duration was from 6 weeks to 6 months.

Outcomes of the Meta-Analyses

Both SSNRIs and SSRIs were significantly superior to placebo as regards their analgesic effects (effect size for SSNRIs:

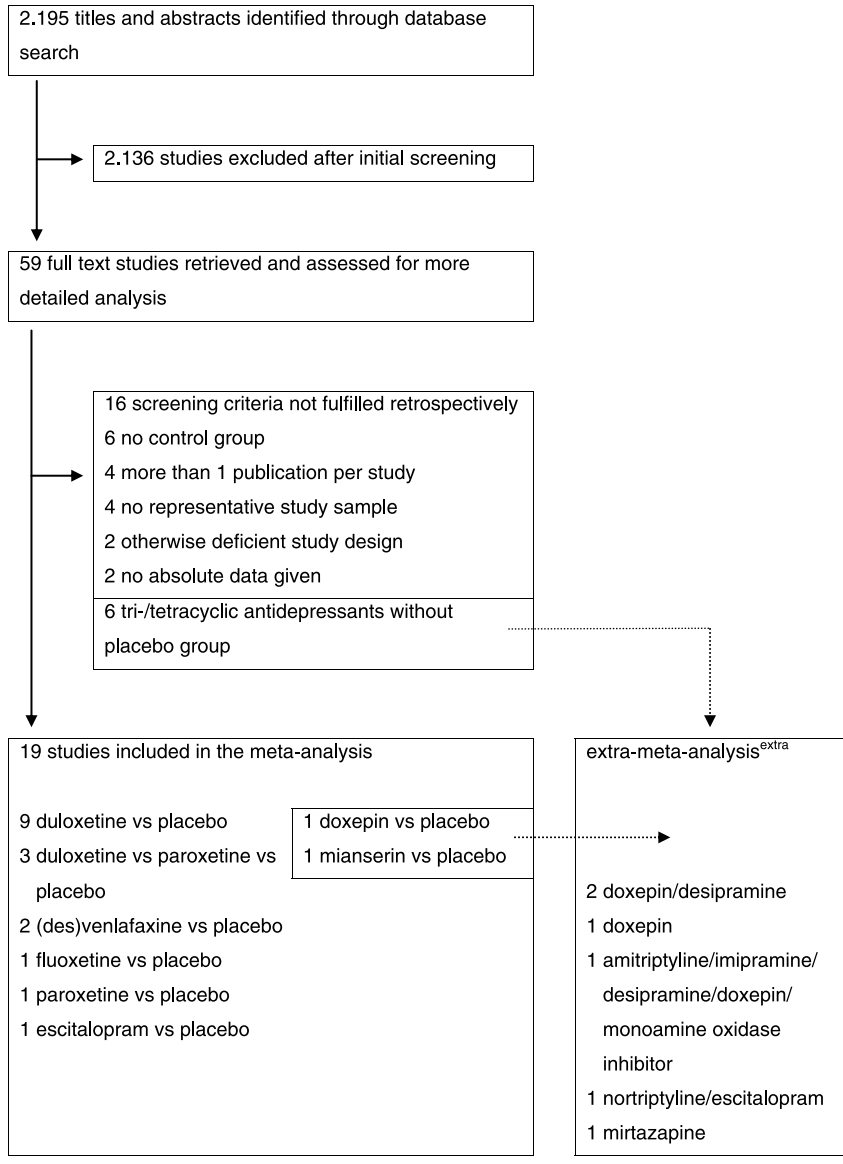

FIGURE 1. Flowchart of selection process. [extra] = non–placebo-controlled TCA studies included in the "extra–meta-analysis" (see Discussion).

0.27 [0.21, 0.33], heterogeneity: $Q = 7.185$, degrees of freedom [*df*] = 13, $P = 0.892$, $I^2 = 0.0\%$; effect size for SSRIs: 0.24 [0.13, 0.36], heterogeneity: $Q = 3.348$, $df = 5$, $P = 0.647$, $I^2 = 0.0\%$; Figs. 2 and 3), whereas TCAs showed no statistically significant difference to placebo (effect size for TCAs: 0.21 [−0.73, 1.14], heterogeneity: $Q = 4.389$, $df = 1$, $P = 0.036$, $I^2 = 77.2\%$; Fig. 4).

All substance classes had a significantly higher AD effect compared with placebo treatment (effect size for SSNRIs: 0.28 [0.22, 0.34], heterogeneity: $Q = 12.701$, $df = 13$, $P = 0.471$, $I^2 = 4.3\%$; effect size for SSRIs: 0.27 [0.09, 0.45], heterogeneity: $Q = 5.082$, $df = 3$, $P = 0.279$, $I^2 = 13.9\%$; effect size for TCAs: 0.76 [0.33, 1.18], heterogeneity: $Q = 0.002$, $df = 1$, $P = 0.967$, $I^2 = 0.0\%$; Figs. 2–4). Among the different substance classes, there were no significant differences in both analgesic and AD therapeutic effects.

Outcome of the Correlation Analysis

There was a strong positive correlation of the effect sizes concerning pain and depression for the SSNRI studies ($r = 0.667$; $P = 0.009$; 14 studies). For SSRIs (4 studies) and TCAs (2 studies), no correlations could be calculated because of the small number of placebo-controlled studies.

DISCUSSION

Analysis of the First Hypothesis ("Antidepressants of Different Classes Vary in Their Effects on Painful Symptoms in Depressive Disorders")

The main results suggest that both SSNRIs and SSRIs were significantly superior to placebo as regards their analgesic effects, whereas TCAs showed no statistically significant differences to placebo. The effects were small, however, and no significant differences could be identified, if the analgesic effects of SSNRIs and SSRIs were compared with each other. Thus, the first hypothesis has to be rejected with respect to SSNRIs and SSRIs.

As regards the TCA studies, a final decision cannot be reached yet because of the low number of placebo-controlled

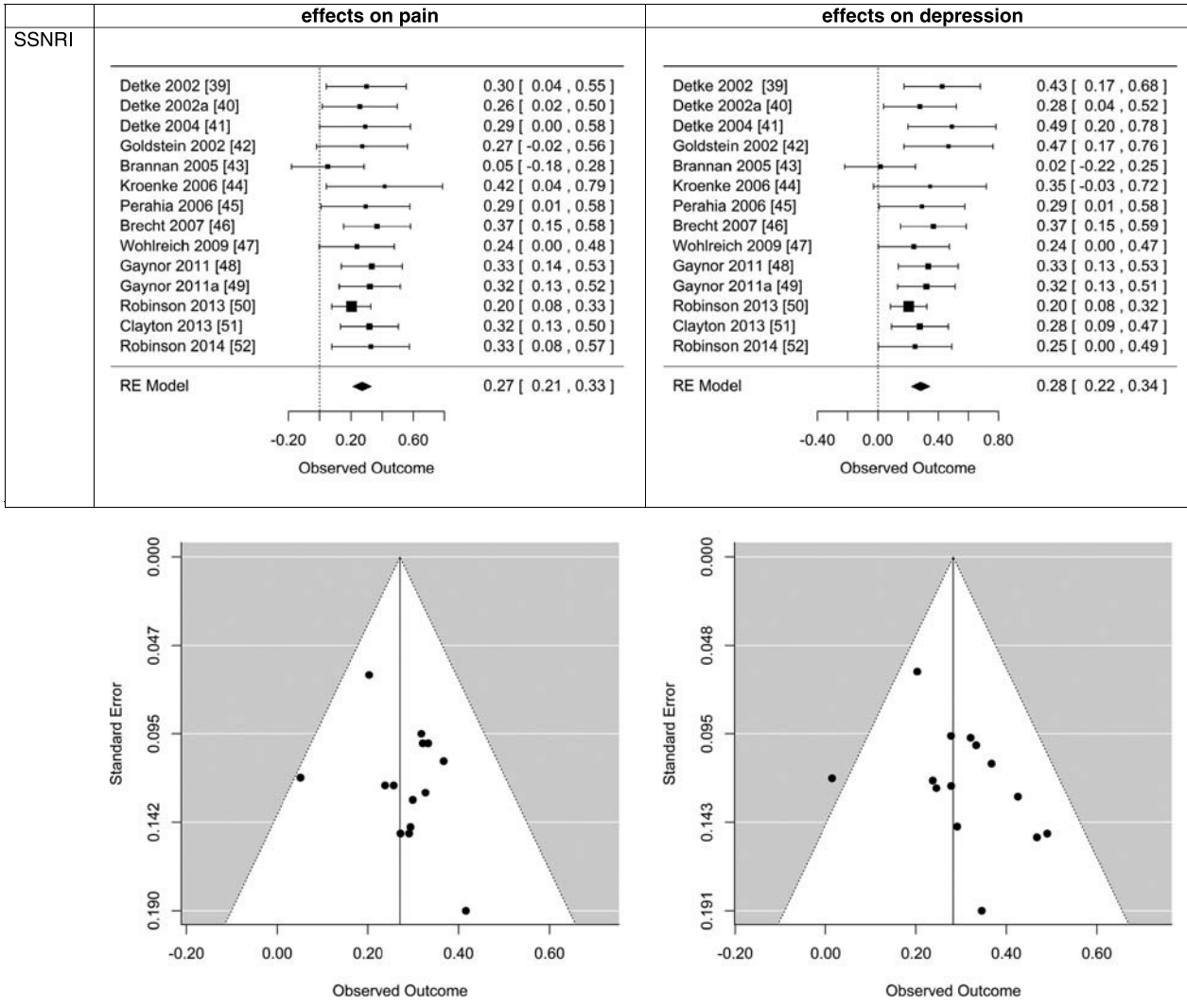

FIGURE 2. Therapeutic effects on pain/depression under SSNRIs (effect size/confidence interval) (above) and the respective funnel plots (below).

studies and the low standard of methodology. For the purpose of obtaining a further perspective for interpretation, a subsequent "extra–meta-analysis" was performed on both placebo-controlled and non–placebo-controlled TCA studies. The non–placebo-controlled TCA studies were those TCA studies that dropped out during the search process because of their missing placebo control group (Fig. 1). For the non–placebo-controlled studies, the placebo arm was replaced by the baseline outcomes, and the *P* values for the paired-samples tests have been transformed into Cohen *d*. Thus, in addition to the 2 placebo-controlled TCA studies (doxepin, n = 30; mianserin, n = 20), 6 non–placebo-controlled TCA studies were included (see Table S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A390) with further 1056 participants, of whom 594 received mirtazapine, 407 doxepin/desipramine/amitriptyline/imipramine/nortriptyline, and 29 received no treatment at all; a further 30 patients were treated with escitalopram as a control group. In 3 of these non–placebo-controlled TCA studies, the outcome data on depression scores were not sufficient.[56,57,60,64] In 4 of these studies, the minimum observation period of 6 weeks was not fulfilled, as it was only 4 weeks[56–60] (see Table S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A390).

If, however, all these 6 non–placebo-controlled TCA studies were included, TCAs would be significantly superior to placebo/baseline as regards the treatment of pain. The overall effect size for the treatment of pain (0.31 [0.17, 0.44]; heterogeneity: $Q = 10.826$, $df = 7$, $P = 0.146$, $I^2 = 30.0\%$; Fig. 5) would not be significantly higher than the previously mentioned effect sizes of the SSNRI/SSRI studies (0.27 [0.21, 0.33]/0.24 [0.13, 0.36]; Figs. 2 and 3). Thus, if these non–placebo-controlled TCA studies were included, TCAs could also be considered significantly superior to placebo as regards pain relief, with the result that the first hypothesis could also be rejected with respect to this group of ADs.

So far, the so-called "dual-action ADs" (eg, duloxetine, venlafaxine, amitriptyline) that target serotonin and noradrenalin have mostly been used in clinical practice to treat depression with comorbid pain, although sufficient evidence is still missing. This clinical practice is attributable to the hypothesis of a functional reduction of the descending inhibitory pathways in depression, which is related to serotonin and noradrenalin. Both neurotransmitters are supposed to be reduced in their concentration during depression, as well as neuromodulators such as opioid peptides

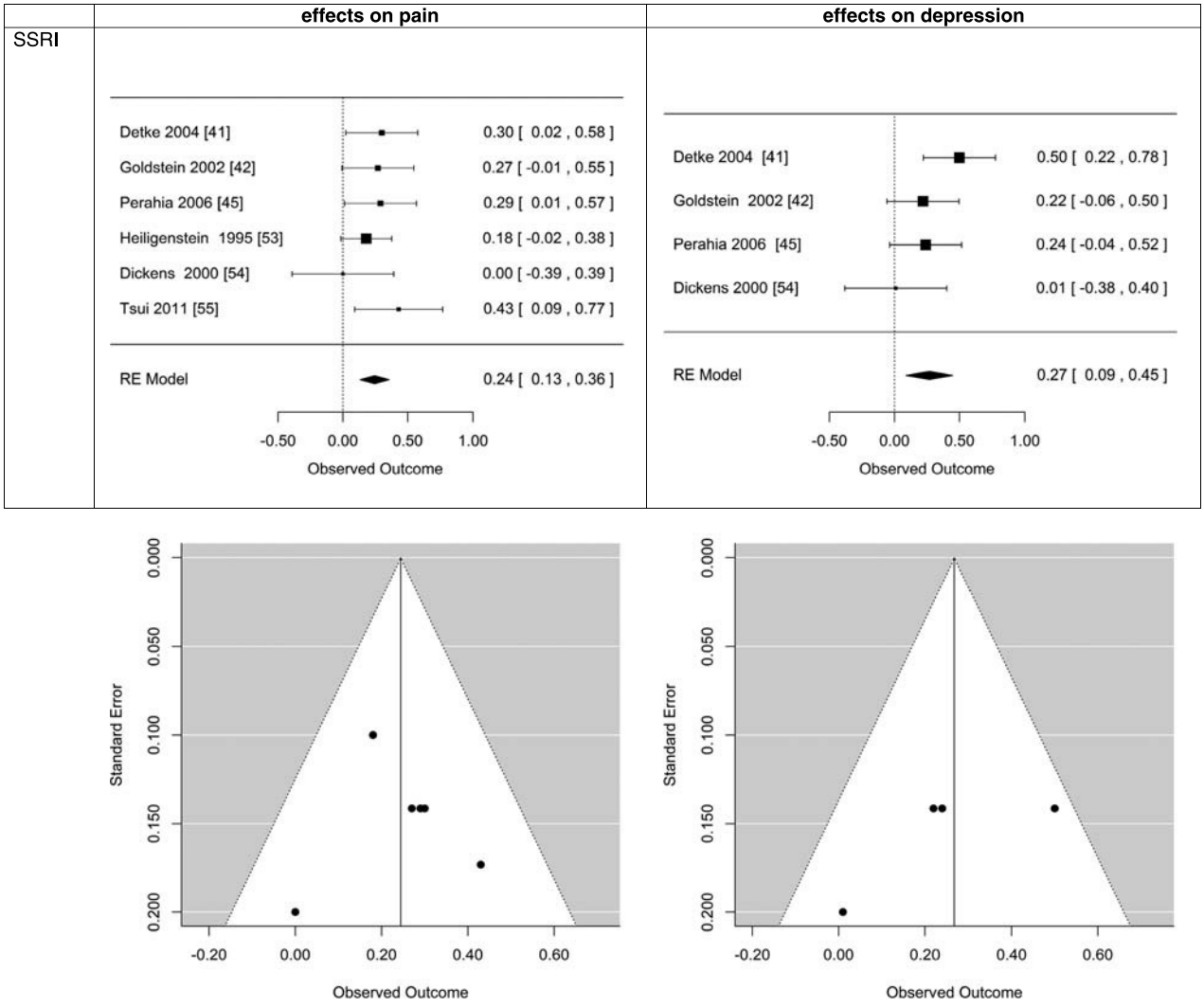

FIGURE 3. Therapeutic effects on pain/depression under SSRIs (effect size/confidence interval) (above) and the respective funnel plots (below).

among other mechanisms.[18–21] The descending inhibitory pathways theory is strengthened by the finding of increased experimental pain thresholds and simultaneously increased clinical pain symptoms in depressed patients.[21,22] Both phenomena could be explained by nociceptive stimuli being processed less at spinal and subcortical level, a deficiency that may lead then to both a hypalgesia and an insufficient activation of pain inhibitory systems.[21] According to a clinical investigation using a neuroendocrine challenge paradigm, an involvement of serotoninergic dysfunction underlying altered pain perception in depression has been suggested.[19] However, according to the discussion in current research, other substances (eg, γ-aminobutyric acid, glycine, opioids) as well as specific plasticity factors (eg, ON/OFF cells) have been undervalued.[23–25] Recent theories point more to complex interactions of different parameters and, in the case of the cortex, to a cortical "matrix" rather than to a "pain center."[23] On this basis, our finding of more or less comparable analgesic effects of all ADs in patients with depressive disorders seems to have a more plausible explanation. Nevertheless, as a common principle, all included types of ADs have a serotonergic component.

Analysis of the Second Hypothesis ("Antidepressant Drugs Have a Noticeable Effect on the Pain Symptoms in Depressive Disorders")

Similarly, the second hypothesis is hardly sustainable considering the small effect sizes as regards pain relief. Thus, effects on pain are detectable, but with low markedness. The results are comparable to previous meta-analyses of studies on painful physical symptoms,[34–36] which did not include TCA studies:

(1) According to a meta-analysis of 8 studies, both duloxetine and paroxetine showed no difference in pain outcomes, but both drugs were superior to placebo with overall small effects, so that the clinical significance of this finding is judged to be uncertain.[34]
(2) Another meta-analysis[35] included 5 trials on duloxetine and found only very small and not significant analgesic effects.
(3) In a meta-analysis on 11 acute, double-blind, placebo-controlled studies, duloxetine showed significant but small effect sizes in reducing painful physical symptoms (0.26) and depressive symptoms (0.25).[36]

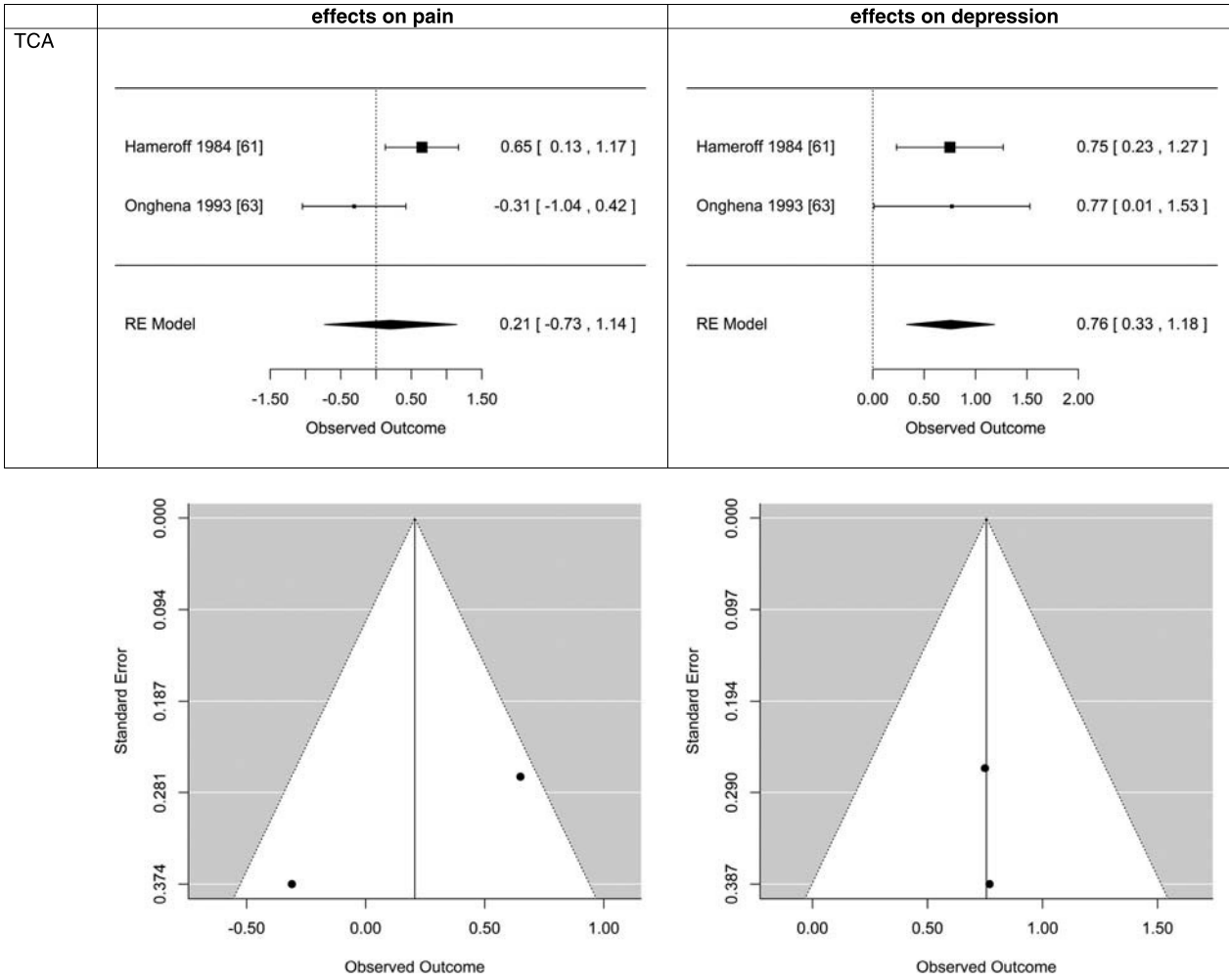

FIGURE 4. Therapeutic effects on pain/depression under TCAs (effect size/confidence interval) (above) and the respective funnel plots (below).

Further, a systematic Cochrane review revealed a higher dropout rate due to any cause in the patients randomized to duloxetine when compared with escitalopram or venlafaxine.[72] Furthermore, the authors report weak evidence suggesting that patients taking duloxetine experienced more adverse events than did those taking paroxetine.

The small effect sizes according to the classification of Cohen[37] lead to the assumption that in depressive disorders the treatment of pain with drugs should not form the only treatment strategy. Of course, medications other than ADs might give additional support (eg, pregabalin), but the current state is not convincing. In particular, opioids are contraindicated.[65]

Apart from pharmacotherapy, a specified psychotherapy focusing on psychoeducation and cognitive-behavioral, emotional, and psychosocial aspects, as well as attachment strategies, ought to play a much more important role in the successful treatment of pain in depressive disorders, as it is known for other psychosomatic pain disorders. For example, in somatoform pain disorders, strong effect sizes were achieved in a group psychotherapy approach.[66] However, only few psychotherapy studies have been performed to treat pain in depression. There is, however, already some evidence for their success in the treatment of chronic pain, for example, for the use of acceptance-based interventions such as stress reduction programs based on mindfulness or acceptance and commitment therapy.[67,68] Also complementary therapeutic approaches, which are nonpharmacological, such as physical activity, mindfulness training, music therapy, or multimodal approaches, might each yield a comparable or even higher effect in this clinical population.[69–71] However, as a remarkable bias, very few nonpharmacological studies are being performed.

Analysis of the Third Hypothesis ("There Is a Positive Correlation Between the Therapeutic Effects on Symptoms of Depression and on Those of Pain")

The third hypothesis could be confirmed for the SSNRIs: a strong positive correlation between the effect sizes of analgesic and AD treatment could be detected for the SSNRI studies ($r = 0.667$; $P = 0.009$; 14 studies). For SSRIs (4 studies) and TCAs (2 studies), no correlations could be calculated because of the small number of placebo-controlled studies. If all studies could be taken together, including non–placebo-controlled studies used in the extra–meta-analysis but excluding 1 ambiguous study[63] (Fig. 4) with a low number of participants (n = 20), a strong correlation ($r = 0.799$; $P < 0.001$; 22 studies) would be found (see Figure S6, Supplemental Digital Content 2, http://links.lww.com/JCP/A391). This suggests the AD effect—probably independent

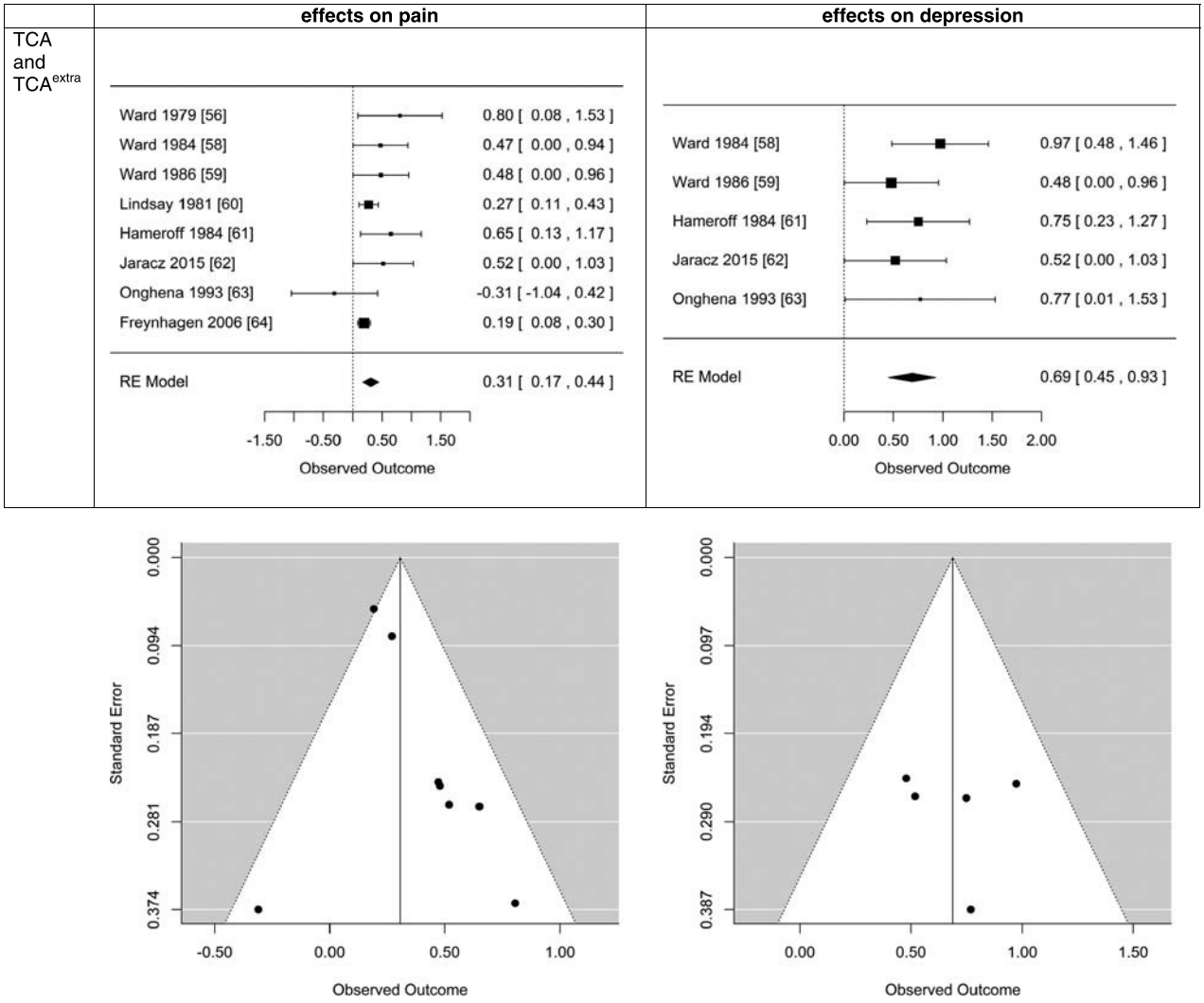

FIGURE 5. Therapeutic effects on pain/depression under TCAs including, in addition, non–placebo-controlled studies (effect size/confidence interval) (above) and the respective funnel plots (below). ^{extra} = "extra–meta-analysis" (see Discussion).

of the used drug class (as long as it is effective on depression)—to be the most important factor for pain relief in patients with primary depressive disorders. However, the poor study data situation for the SSRI and TCA studies (and the according questionable method of this subsequent extra–meta-analysis) has to be kept in mind.

Clinical Implications

The findings that therapeutic effects on depressive and painful symptoms show a correlation (see Fig. S6, Supplemental Digital Content 2, http://links.lww.com/JCP/A391) and that there seem to be no substantial differences between the various types of ADs (in particular SSNRIs and SSRIs) suggest that treating depression is—at least at the end point of the treatment—equivalent with treating the painful symptoms associated with it. Thus, if pain represents a symptom within mood depression, a good AD treatment should lead to pain relief parallel to the remission of the depressive symptoms. This underlines the importance of proper diagnosis and treatment of depression in patients presenting with painful symptoms. Clinicians can choose the appropriate AD according to the requirements of the single individual and also according to potential adverse events. The overall interpretation of our results suggests that the current empirical state of research does not generally allow the preference of specific ADs before others for the treatment of pain symptoms in depression. As well, the initiation of a specific analgesics treatment regimen seems not to be necessary as long as the remission of the depressive disorders has not been reached.

Excursus on Primary Pain Disorders

In patients with primary pain disorders with comorbid depressive symptoms, the situation seems to be different. For example, SSNRIs have been supposed to be more effective on neuropathic pain than SSRIs.[73] The latter effect has been attributed to a direct mechanism of action of ADs with an accordingly earlier onset of the analgesic effect compared with an indirect mechanism and later AD (and therefore also analgesic) effect in the case of pain as a symptom of depression (eg, see Torta and Ieraci[74]). Duloxetine has been proven to show adequate amounts of moderate-quality evidence from 8 studies that doses of 60 and 120 mg daily are efficacious for treating pain in diabetic peripheral neuropathy.[73] Tricyclic ADs have also repeatedly been shown to be effective in neuropathic pain in numerous controlled trials.[33] However, recent Cochrane analyses found only little

compelling evidence to support the use of venlafaxine and nearly no sufficient evidence for the therapeutic effect of amitriptyline in neuropathic pain.[75,76]

Because of methodological reasons, our results, which derived exclusively from patients with depressive disorders, are not transferable to patients with primary pain disorders, not to mention nondepressed individuals suffering from pain.

Implications on Pathophysiology

From a pathophysiological point of view, the strong correlation might give a further hint that pain is a core symptom of major depression instead of a comorbid disorder, which is underlined by epidemiological studies. Ohayon and Schatzberg[3] refer to pain being unexplained by a medical disorder. It has to be mentioned that we focused on patients with depressive disorders and not related disorders such as neuropathic pain, somatoform pain disorders, or other psychosomatic pain disorders. Accordingly, it appears obvious that the normalization of pain perception starts with the reduction of a depressed mood, which mirrors the strong correlation of pain and depression. Because we had no sufficient data on the time in which the analgesic effects were achieved, direct and indirect analgesic effects cannot be differentiated. However, even if analgesic and AD effects had a less predictive association and would be considered, therefore, as largely independent of each other, they seem to merge, nevertheless—in case of depression—into a common final pathway, which can be explained by a close relationship of both entities depression and pain (see first part of the article). Accordingly, one could hypothesize the existence of a "primary independence" of sensory and affective processing pathways and a "final association" of sensory and affective states in the sense of an indirect bidirectional interplay.

Relationships between the reduction of depression and pain have already been described in the 1970s and 1980s.[56,57,59] In former studies, the change of the severity of the depression has been shown to be a strong predictor for the severity of pain and vice versa.[77,78] In contrast, an evaluation of the relationship of pain and depression in 6 placebo-controlled trials with duloxetine[79] suggested a very low predictive association between analgesic and AD effects of duloxetine: the percentage of variability in changes of depression scores explained by pain relief ranged from 3.8% to 19.6% (dependent on dosage and type of pain) with similar findings for the placebo group. As in previous studies described, an earlier onset of the analgesic effect compared with the AD effect was found: although the AD effect began 7 to 16 days later than the analgesic effect, the association between changes in pain and depression measures, at the point in time at which a significant analgesic response is first achieved, decreased when compared with the association between changes in measures at study end points. The authors conclude that the AD and the analgesic responses are largely independent of each other.[79] They believe that the sensory and affective aspects of pain may be independently processed as there are respective findings of functional imaging studies in fibromyalgia, which suggest that there is objective evidence of amplification of the sensory dimension in pain.[80] However, the placebo group responded similarly to duloxetine with analgesia first, followed by an AD response. Therefore, the authors speculate that in depressed patients with pain the natural course of improvement involves lessening of pain followed by depression improvement. There is also some evidence that ADs that appear to have no analgesic effect in nondepressed pain patients do lower pain scores in depressed pain patients.[79,81]

One study included in the present meta-analysis showed that in 50.6% of cases the reduction of pain through duloxetine was independent of the improvement in depressive symptoms, whereas in 49.4% pain reduction was an indirect effect mediated through reduction in the depression symptoms.[82] In other studies, a good analgesic response was associated with a greater reduction of symptoms of depression[48–50,62] (see Table S1, Supplemental Digital Content 1, http://links.lww.com/JCP/A390). In a recent study,[50] a path analysis indicated that the likelihood of remission of symptoms of depression was in 16% directly due to the treatment, in 41% due to pain reduction, and in 43% due to functional improvement.

LIMITATIONS

The present study has some limitations. First, the methodological quality of most of the TCA studies is poor, so that only 2 placebo-controlled TCA studies could be included. In this meta-analysis, as regards the degree of pain relief, a high heterogeneity among the TCA studies was found ($I^2 < 77.2\%$), whereas heterogeneity values for the other substance classes were overall good ($I^2 < 13.9\%$).

In order to discuss our results and to imagine possible tendencies in the TCA studies if the statistical power was enhanced, we explored data according to an additional meta-analysis calculation on TCA studies that also considered non–placebo-controlled TCA studies ("extra–meta-analysis"). Hereby, the therapeutic effect of TCAs on pain was not significantly higher than that of SSNRIs and SSRIs, with moderate heterogeneity ($I^2 = 30.0\%$). This consecutive calculation has a weak methodological basis and has to be interpreted with caution. Conclusions cannot be drawn from this additional calculation, but some tendencies might be assessed. In addition, a limitation is that we did not perform comparable, non–placebo-controlled studies including meta-analyses on SSNRIs and SSRIs because fact that there are sufficiently elaborated placebo-controlled studies available. Nevertheless, this extra–meta-analysis might give another illustration of the clinical situation. Thereby it should be kept in mind that the extra–meta-analysis does not belong to the main meta-analysis but serves the overall discussion by providing some additional data on a—certainly—questionable empirical basis. The low statistical value of the TCA studies reflects the situation of the current state of research in this field.

Second, the therapeutic effect sizes as regards the relief of symptoms of depression, which were assessed in the present meta-analysis, can only be interpreted in the context of the correlation between therapeutic effects on pain and depression, because studies on the efficacy of AD treatment on patients without evaluated pain symptoms have not been included in this meta-analysis.

Furthermore, dosage effects could not be considered, although they may play a significant role. In all studies investigating SSRIs, minimum dosages were used (paroxetine 20 mg/d, fluoxetine 20 mg/d, escitalopram 10 mg/d), as well as in 1 venlafaxine study (50 mg/d[51]), whereas the studies on duloxetine and TCAs showed a trend toward higher dosages (duloxetine between 60 and 120 mg/d, doxepin 200 mg/d, mianserin 90 mg/d).

Although only patients with a depressive disorder have been included in the present meta-analysis, participants often showed comorbid diagnoses, reflecting rather the natural clinical situation than an experimental setting. Furthermore, in every study included in the current meta-analysis, some patients did not experience painful symptoms at baseline. This means that higher analgesic effects could have been expected in both placebo and control groups, if only those patients with both depression and pain symptoms at baseline had been included.

STRENGTHS

Despite its limitations the study has 3 main strengths. First, the study focuses on the influence of ADs on pain relief in

primarily depressive disorders, whereas most comparable research data refer to primarily pain disorders. Second, for the first time, TCA studies are included, which is of importance in the light of widespread use of TCAs for patients with pain symptoms. Third, using the correlation data, the study gives further insight into the interplay of AD and analgesic aspects in a relatively large number of patients.

CONCLUSIONS

To our knowledge, this is the first independent meta-analysis of the therapeutic effects of ADs including SSNRIs, SSRIs, and TCAs on pain symptoms in depressive disorders. The results suggest an overall small therapeutic effect of the ADs as regards pain relief in patients with depressive disorders and no relevant differences among SSNRIs and SSRIs. Selective serotonin-noradrenaline reuptake inhibitors and SSRIs were significantly superior to placebo as regards pain, whereas TCAs showed no differences to placebo. However, there are only few placebo-controlled studies using TCAs. If the results of non–placebo-controlled studies using TCAs were included, the results would be comparable to those of SSRIs and SSNRIs.

An altered pain perception in depressive disorders is well known. Thus, the treatment of the depressive disorder is primary. The positive correlation of the effect sizes of pain and depression treatment leads to the assumption that a successful AD treatment should lead to pain relief parallel to the remission of the depressive symptoms, possibly independent of the type of AD used. From a theoretical point of view, this might especially apply to the pain symptoms of depression, to a lesser extent to comorbid pain diseases in depression. In particular, no data on primary pain disorders with consecutive depressive symptoms/disorders have been evaluated in the current investigation. Thus, data presented here refer to the treatment only of primary depressive disorders with pain symptoms, not to pain disorders with comorbid depression.

Further studies of high methodological quality are urgently warranted comparing different classes of ADs or other potential drugs as well as nonpharmacological interventions and their effects on clinically relevant pain relief in depressive patients, particularly in view of the large number of people affected worldwide.

ACKNOWLEDGMENTS

The authors thank Prof Stefan Lautenbacher, Bamberg/Germany, and Prof Martin T. Huber, Stade/Germany, for providing the theoretical framework of this study, and Prof Jürgen-Christian Krieg, Marburg/Germany, Dr Corinna Illingworth, and Peter Illingworth for proofreading and for their helpful, critical comments. They also thank the library of the Psychiatric Center Nordbaden Wiesloch/Germany for providing literature.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

REFERENCES

1. Linden M. Epidemology and treatment of depressive disorders [in German]. *Z Psychosom Med Psychother*. 2003;49:333–345.
2. Spiessl H, Hubner-Liebermann B, Hajak G. Depression, a widespread disease. Epidemiology, care situation, diagnosis, therapy and prevention [in German]. *Dtsch Med Wochenschr*. 2006;131:35–40.
3. Ohayon MM, Schatzberg AF. Chronic pain and major depressive disorder in the general population. *J Psychiatr Res*. 2010;44:454–461.
4. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry*. 2003;60:39–47.
5. Lépine JP, Briley M. The epidemiology of pain in depression. *Hum Psychopharmacol*. 2004;19(suppl 1):S3–S7.
6. Polatin PB, Kinney RK, Gatchel RJ, et al. Psychiatric illness and chronic low-back pain. The mind and the spine—which goes first? *Spine (Phila Pa 1976)*. 1993;18:66–71.
7. Garcia-Cebrian A, Gandhi P, Demyttenaere K, et al. The association of depression and painful physical symptoms—a review of the European literature. Eur Psychiatry 2006;21:379–388.
8. Geerlings SW, Twisk JW, Beekman AT, et al. Longitudinal relationship between pain and depression in older adults: sex, age and physical disability. *Soc Psychiatry Psychiatr Epidemiol*. 2002;37:23–30.
9. Bair MJ, Robinson RL, Eckert GJ, et al. Impact of pain on depression treatment response in primary care. *Psychosom Med*. 2004;66:17–22.
10. Fishbain DA, Cutler R, Rosomoff HL, et al. Chronic pain associated depression: antecedent or consequence of chronic pain? A review. *Clin J Pain*. 1997;13:116–137.
11. Fava M. Somatic symptoms, depression, and antidepressant treatment. *J Clin Psychiatry*. 2002;63:305–307.
12. Seemann H, Zimmermann M. Regulationsmodell des Schmerzes aus systemtheoretischer Sicht-Eine Standortbestimmung. In: Basler HD, Franz C, Kröner-Herwig B, Rehfisch HP, Seemann H, eds. *Psychologische Schmerztherapie*. 4*Auflage*. Springer Berlin, Heidelberg, NewYork ed. 1998:23–58.
13. Robinson MJ, Edwards SE, Iyengar S, et al. Depression and pain. *Front Biosci (Landmark Ed)*. 2009;14:5031–5051.
14. Walker AK, Kavelaars A, Heijnen CJ, et al. Neuroinflammation and comorbidity of pain and depression. *Pharmacol Rev*. 2014;66:80–101.
15. Price ML, Curtis AL, Kirby LG, et al. Effects of corticotropin-releasing factor on brain serotonergic activity. *Neuropsychopharmacology*. 1998;18:492–502.
16. Kirby LG, Rice KC, Valentino RJ. Effects of corticotropin-releasing factor on neuronal activity in the serotonergic dorsal raphe nucleus. *Neuropsychopharmacology*. 2000;22:148–162.
17. Tomoda A, Suzuki H, Rabi K, et al. Reduced prefrontal cortical gray matter volume in young adults exposed to harsh corporal punishment. *Neuroimage*. 2009;47(suppl 2):T66–T71.
18. Gebhardt S, Lautenbacher S. Pain in depressive disorders. In: Marchand S, Saravane D, Gaumond I, eds. *Mental Health and Pain. Somatic and Psychiatric Components of Pain in Mental Health*. Heidelberg, Germany: Springer; 2014:99–117.
19. Kundermann B, Hemmeter-Spernal J, Strate P, et al. Pain sensitivity in major depression and its relationship to central serotoninergic function as reflected by the neuroendocrine response to clomipramine. *J Psychiatr Res*. 2009;43:1253–1261.
20. Millan MJ. Descending control of pain. *Prog Neurobiol*. 2002;66:355–474.
21. Lautenbacher S, Krieg JC. Pain perception in psychiatric disorders: a review of the literature. *J Psychiatr Res*. 1994;28:109–122.
22. Bär KJ, Greiner W, Letsch A, et al. Influence of gender and hemispheric lateralization on heat pain perception in major depression. *J Psychiatr Res*. 2003;37:345–353.
23. Heinricher MM, Tavares I, Leith JL, et al. Descending control of nociception: specificity, recruitment and plasticity. *Brain Res Rev*. 2009;60:214–225.
24. Mendell LM. Constructing and deconstructing the gate theory of pain. *Pain*. 2014;155:210–216.
25. Todd AJ. Plasticity of inhibition in the spinal cord. *Handb Exp Pharmacol*. 2015;227:171–190.
26. Lanquillon S, Krieg JC, Bening-Abu-Shach U, et al. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology*. 2000;22:370–379.

27. Carter GT, Sullivan MD. Antidepressants in pain management. *Curr Opin Investig Drugs*. 2002;3:454–458.
28. Gebhardt S, Heiser P, Fischer S, et al. Relationships among endocrine and signaling-related responses to antidepressants in human monocytic U-937 blood cells: analysis of factors and response patterns. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32:1682–1687.
29. Holsboer F, Barden N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. *Endocr Rev*. 1996;17: 187–205.
30. Feuerstein TJ. Chronic pain treatment with antidepressants—metaanalysis [in German]. *Schmerz*. 1997;11:213–226.
31. Delgado PL. Common pathways of depression and pain. *J Clin Psychiatry*. 2004;65(suppl 12):16–19.
32. Fields HL, Basbaum AI, Heinricher MM. Central nervous system mechanisms of pain modulation. In: McMahon S, Koltzenburg M, eds. *Textbook of Pain*. 5th ed. Burlington, MA: Elsevier Health Sciences; 2005: 125–142.
33. Sindrup SH, Otto M, Finnerup NB, et al. Antidepressants in the treatment of neuropathic pain. *Basic Clin Pharmacol Toxicol*. 2005;96:399–409.
34. Krebs EE, Bradley NG, Gartlehner G, et al. Treating the physical symptoms of depression with second-generation antidepressants: a systematic review and metaanalysis. *Psychosomatics*. 2008;49:191–198.
35. Spielmans GI. Duloxetine does not relieve painful physical symptoms in depression: a meta-analysis. *Psychother Psychosom*. 2008;77:12–16.
36. Ball SG, Desaiah D, Spann ME, et al. Efficacy of duloxetine on painful physical symptoms in major depressive disorder for patients with clinically significant painful physical symptoms at baseline: a meta-analysis of 11 double-blind, placebo-controlled clinical trials. *Prim Care Companion CNS Disord*. 2011;13.
37. Cohen J. A power primer. *Psychol Bull*. 1992;112:155–159.
38. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw*. 2010;36:1–48.
39. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial. *J Clin Psychiatry*. 2002;63:308–315.
40. Detke MJ, Lu Y, Goldstein DJ, et al. Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression. *J Psychiatr Res*. 2002;36:383–390.
41. Detke MJ, Wiltse CG, Mallinckrodt CH, et al. Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Neuropsychopharmacol*. 2004;14: 457–470.
42. Goldstein DJ, Mallinckrodt C, Lu Y, et al. Duloxetine in the treatment of major depressive disorder: a double-blind clinical trial. *J Clin Psychiatry*. 2002;63:225–231.
43. Brannan SK, Mallinckrodt CH, Brown EB, et al. Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder. *J Psychiatr Res*. 2005;39:43–53.
44. Kroenke K, Messina N 3rd, Benattia I, et al. Venlafaxine extended release in the short-term treatment of depressed and anxious primary care patients with multisomatoform disorder. *J Clin Psychiatry*. 2006;67:72–80.
45. Perahia DG, Wang F, Mallinckrodt CH, et al. Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial. *Eur Psychiatry*. 2006;21:367–378.
46. Brecht S, Courtecuisse C, Debieuvre C, et al. Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial. *J Clin Psychiatry*. 2007;68:1707–1716.
47. Wohlreich MM, Sullivan MD, Mallinckrodt CH, et al. Duloxetine for the treatment of recurrent major depressive disorder in elderly patients: treatment outcomes in patients with comorbid arthritis. *Psychosomatics*. 2009;50:402–412.
48. Gaynor PJ, Gopal M, Zheng W, et al. A randomized placebo-controlled trial of duloxetine in patients with major depressive disorder and associated painful physical symptoms. *Curr Med Res Opin*. 2011;27: 1849–1858.
49. Gaynor PJ, Gopal M, Zheng W, et al. Duloxetine versus placebo in the treatment of major depressive disorder and associated painful physical symptoms: a replication study. *Curr Med Res Opin*. 2011;27: 1859–1867.
50. Robinson MJ, Sheehan D, Gaynor PJ, et al. Relationship between major depressive disorder and associated painful physical symptoms: analysis of data from two pooled placebo-controlled, randomized studies of duloxetine. *Int Clin Psychopharmacol*. 2013;28:330–338.
51. Clayton AH, Kornstein SG, Dunlop BW, et al. Efficacy and safety of desvenlafaxine 50 mg/d in a randomized, placebo-controlled study of perimenopausal and postmenopausal women with major depressive disorder. *J Clin Psychiatry*. 2013;74:1010–1017.
52. Robinson M, Oakes TM, Raskin J, et al. Acute and long-term treatment of late-life major depressive disorder: duloxetine versus placebo. *Am J Geriatr Psychiatry*. 2014;22:34–45.
53. Heiligenstein JH, Ware JE Jr, Beusterien KM, et al. Acute effects of fluoxetine versus placebo on functional health and well-being in late-life depression. *Int Psychogeriatr*. 1995;7(suppl):125–137.
54. Dickens C, Jayson M, Sutton C, et al. The relationship between pain and depression in a trial using paroxetine in sufferers of chronic low back pain. *Psychosomatics*. 2000;41:490–499.
55. Tsui JI, Herman DS, Kettavong M, et al. Escitalopram is associated with reductions in pain severity and pain interference in opioid dependent patients with depressive symptoms. *Pain*. 2011;152:2640–2644.
56. Ward NG, Bloom VL, Friedel RO. The effectiveness of tricyclic antidepressants in the treatment of coexisting pain and depression. *Pain*. 1979;7:331–341.
57. Ward NG, Bloom VL, Dworkin S, et al. Psychobiological markers in coexisting pain and depression: toward a unified theory. *J Clin Psychiatry*. 1982;43(8 pt 2):32–41.
58. Ward N, Bokan JA, Phillips M, et al. Antidepressants in concomitant chronic back pain and depression: doxepin and desipramine compared. *J Clin Psychiatry*. 1984;45(3 pt 2):54–59.
59. Ward NG. Tricyclic antidepressants for chronic low-back pain. Mechanisms of action and predictors of response. *Spine*. 1986;11:661–665.
60. Lindsay PG, Wyckoff M. The depression-pain syndrome and its response to antidepressants. *Psychosomatics*. 1981;22:576–577.
61. Hameroff SR, Weiss JL, Lerman JC, et al. Doxepin's effects on chronic pain and depression: a controlled study. *J Clin Psychiatry*. 1984;45(3 pt 2): 47–53.
62. Jaracz J, Gattner K, Moczko J, et al. Comparison of the effects of escitalopram and nortriptyline on painful symptoms in patients with major depression. *Gen Hosp Psychiatry*. 2015;37:36–39.
63. Onghena P, de Cuyper H, van Houdenhove B, et al. Mianserin and chronic pain: a double-blind placebo-controlled process and outcome study. *Acta Psychiatr Scand*. 1993;88:198–204.
64. Freynhagen R, Muth-Selbach U, Lipfert P, et al. The effect of mirtazapine in patients with chronic pain and concomitant depression. *Curr Med Res Opin*. 2006;22:257–264.
65. Werber A, Schiltenwolf M. Morphine werden immer sorgloser verschrieben. *Dtsch Arztebl Int*. 2015;112:87–88.
66. Nickel R, Ademmer K, Egle UT. Manualized psychodynamic interactional group therapy for the treatment of somatoform pain disorders. *Bull Menninger Clin*. 2010;74:219–237.
67. Chiesa A, Serretti A. Mindfulness-based interventions for chronic pain: a systematic review of the evidence. *J Altern Complement Med*. 2011;17: 83–93.

68. Veehof MM, Oskam MJ, Schreurs KM, et al. Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. *Pain*. 2011;152:533–542.

69. Rosenbaum S, Tiedemann A, Sherrington C, et al. Physical activity interventions for people with mental illness: a systematic review and meta-analysis. *J Clin Psychiatry*. 2014;75:964–974.

70. Gebhardt S, Huber MT, von Georgi R. Effects of music on tonic heat pain in depression—a preliminary investigation. Pain Relief Rep 2014;1. http://dx.doi.org/10.7243/2057-3219-1-1.

71. Bawa FL, Mercer SW, Atherton RJ, et al. Does mindfulness improve outcomes in patients with chronic pain? Systematic review and meta-analysis. *Br J Gen Pract*. 2015;65:e387–e400.

72. Cipriani A, Koesters M, Furukawa TA, et al. Duloxetine versus other anti-depressive agents for depression. *Cochrane Database Syst Rev*. 2012;10:CD006533.

73. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev*. 2014;1:CD007115.

74. Torta RG, Ieraci V. Pharmacological management of depression in patients with cancer: practical considerations. *Drugs*. 2013;73:1131–1145.

75. Gallagher HC, Gallagher RM, Butler M, et al. Venlafaxine for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2015;8:CD0110918.

76. Moore RA, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2015;7:CD008242.

77. Kroenke K, Wu J, Bair MJ, et al. Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. *J Pain*. 2011;12:964–973.

78. Schneider E, Linden M, Weigmann H, et al. Early reduction in painful physical symptoms is associated with improvements in long-term depression outcomes in patients treated with duloxetine. *BMC Psychiatry*. 2011;11:150.

79. Fishbain DA, Detke MJ, Wernicke J, et al. The relationship between antidepressant and analgesic responses: findings from six placebo-controlled trials assessing the efficacy of duloxetine in patients with major depressive disorder. *Curr Med Res Opin*. 2008;24:3105–3115.

80. Cook DB, Lange G, Ciccone DS, et al. Functional imaging of pain in patients with primary fibromyalgia. *J Rheumatol*. 2004;364–378.

81. Max MB, Lynch SA, Muir J, et al. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropaty. *N Engl J Med*. 1992;326:1250–1256.

82. Fava M, Mallinckrodt CH, Detke MJ, et al. The effect of duloxetine on painful physical symptoms in depressed patients: do improvements in these symptoms result in higher remission rates? *J Clin Psychiatry*. 2004;65:521–530.