Antidepressants are used widely to treat depression after stroke, despite limited evidence for their efficacy in this context. Some small studies suggest that prophylactic treatment with antidepressants may prevent the development of depression in select patients. More recently, there has been some excitement about the potential role of selective serotonin reuptake inhibitors (SSRIs) in promoting motor recovery after stroke in patients who are not depressed. The Fluoxetine in Motor Recovery of Patients With Acute Ischemic Stroke (FLAME) trial was a double-blind, placebo-controlled, multicenter trial that randomized patients with ischemic stroke and unilateral motor weakness to fluoxetine 20 mg daily or placebo for 3 months. At day 90, the improvement in the Fugl Meyer motor score from baseline was significantly greater in the fluoxetine group. Also, the frequency of independent patients (modified Rankin Scale: 0–2) was significantly higher in the fluoxetine group (29% versus 9%; \( P = 0.015 \)) although there were no significant differences at other modified Rankin Scale cutoffs. The evidence for how antidepressants mediate stroke outcomes is at present limited, and there are multiple mechanisms through which such efficacy might be acting. Fluoxetine has been reported to attenuate postischemic brain injury by facilitating expression of neuroprotective and regenerative proteins, suppressing poststroke hyperexcitability in unaffected brain, and reducing inflammation. SSRIs may also stimulate neuronal generation, secretion of growth factors that augment neuroplasticity, synaptic plasticity, and expression of brain phosphorylated cAMP response element–binding protein.

**Background and Purpose**—Poststroke depression is a prevalent complication of stroke with unclear pathogenesis. The benefits of antidepressants in this context and their effects on stroke recovery other than effects on mood are not clearly defined, with some studies suggesting efficacy in improving functional outcome in both depressed and nondepressed stroke patients. We have analyzed the preclinical animal data on antidepressant treatment in focal cerebral ischemia, modeled as depression, to help inform clinical trial design.

**Methods**—We performed a systematic review and meta-analysis of data from experiments testing the efficacy of antidepressants versus no treatment to reduce infarct volume or improve neurobehavioral or neurogenesis outcomes in animal models of stroke. We used random-effects metaregression to test the impact of study quality and design characteristics and used trim and fill to assess publication bias.

**Results**—We identified 44 publications describing the effects of 22 antidepressant drugs. The median quality checklist score was 5 of a possible 10 (interquartile range, 4–7). Overall, antidepressants reduced infarct volume by 27.3% (95% confidence interval, 20.7%–33.8%) and improved neurobehavioral outcomes by 53.7% (46.4%–61.1%). There was little evidence for an effect of selective serotonin reuptake inhibitors on infarct volume. For neurobehavioral outcomes there was evidence of publication bias. Selective serotonin reuptake inhibitors were the most frequently studied antidepressant subtype and improved neurobehavioral outcome by 51.8% (38.6%–64.9%) and increased neurogenesis by 2.2 SD (1.3–3.0).

**Conclusions**—In line with current clinical data and despite some limitations, antidepressant treatments seem to improve infarct volume and neurobehavioral outcome in animal models of ischemic stroke. (Stroke. 2014;45:3055-3063.)

**Key Words:** antidepressive agents ■ meta-analysis ■ models, animal ■ review, systematic ■ stroke
and attenuate hypothalamic pituitary axis overactivity, thus reducing cortisol which is associated with poorer outcomes poststroke.

The attrition rate for interventions developed in animal studies before testing in clinical trials suggests that a more systematic approach to translational stroke medicine is required, and this approach has been taken with the EuroHYP-1 (A European, Multicentre, Randomised, Phase III, Clinical Trial of Hypothermia Plus Medical Treatment Versus Best Medical Treatment Alone for Acute Ischaemic Stroke) trial. In the context of the design of a clinical trial testing the efficacy of fluoxetine in stroke, we therefore conducted a systematic review and meta-analysis of data from experiments testing the efficacy of antidepressants in animal models of stroke.

Specifically, we set out to establish whether there were differences between efficacy measured using structural (infarct volume) and functional (neurobehavioral) outcomes which might suggest predominant effects on regeneration and repair rather than on neuronal cell death, the temporal dependence of any observed efficacy, whether efficacy was different in animals exposed to stressful stimuli (which might model aspects of depression), and whether there were data supporting any particular mechanism of action that might be used to refine treatment strategies. We also assessed the extent to which the data presented might be at risk of bias, either through factors relating to experimental design or through publication bias.

Methods

All methods were prespecified in a study protocol which can be accessed at http://www.dcn.ed.ac.uk/camarades/research.html. This study followed the guidelines by Sena et al7 for reporting systematic reviews and meta-analyses of animal studies. We chose infarct size as the primary outcome measure as a more challenging test of efficacy to establish whether antidepressants might have neuroprotective effects which could inform decisions about the timing of treatment in clinical trials, and given that observed effects on neurobehavioral outcome might be confounded by effects on attention and anxiety, influencing performance of tasks. Our secondary outcome measures were effects of antidepressants on neurobehavioral outcome and on neurogenesis.

Search Strategy

We searched 4 online databases (PubMed, Web of Science, BIOSIS, and Embase) in May 2013 using search terms listed in the protocol. Abstracts were screened independently by 2 reviewers (S.K.M. and E.S.S.) to identify those meeting the specified inclusion criteria.

Inclusion and Exclusion Criteria

We included studies that reported the effects of an antidepressant drug in an in vivo animal model of focal cerebral ischemia whether or not depression was also modeled; we therefore included studies that used the chronic mild stress (CMS) paradigm for inducing post-stroke depression. Studies that administered antidepressants both before and after stroke induction were included. Antidepressant drugs were classified as those that are currently prescribed in the United Kingdom for depression or are under investigation as potential antidepressant drugs. We did not include studies that reported the effects of drugs no longer prescribed for depression. We included studies that reported the number of animals per group, outcome as a lesion size (infarct volume or infarct area), neurobehavioral score or neurogenesis measure (proliferation, migration, survival, or differentiation), and the mean and its variance (SEM or SD). Experiments involving cotreatments with additional drugs were excluded. Experiments with environmental enrichment or physical rehabilitation as a cotreatment were included. Data were extracted to the CAMARADES data manager (Microsoft Office Access 2007).

Quality Assessment

We assessed risk of bias using the CAMARADES 10-item quality checklist which comprises (1) publication in a peer-reviewed journal; and reporting of (2) control of temperature, (3) random allocation to groups, (4) allocation concealment (blinded induction of ischemia), (5) blinded assessment of outcome, (6) use of an anesthetic without intrinsic neuroprotective activity (ketamine), (7) the use of comorbid animals, (8) performing a sample size calculation, (9) compliance with animal welfare regulations, and (10) a statement of potential conflicts of interest.

Data Extraction

We extracted data for study design elements including the time, route, and dose of the drug administration, the species, sex and strain of the animal, the type of ischemia (permanent, temporary or thrombotic), the anesthetic and ventilation method used during the induction of injury, and the type of neurobehavioral test used and time of assessment.

For each comparison, we extracted data describing the number of animals per group, the mean outcome, and the variance for both the control and treatment group. When a single control group was used for multiple treatment groups, the impact of this control group was adjusted by dividing the number of animals by the number of treatment groups served. Where data were not reported, we contacted authors seeking further information.

Where data were reported graphically, we used digital ruler software (Universal Desktop Ruler, AVPSoft.com) to ascertain values, and where data for a single animal group were reported at different times, we only extracted data for the final time point. If it was unclear whether the measure of variance reported was SD or SEM, we assumed that the measure used was SEM, because otherwise a study might be given undue weight in the meta-analysis. All data were extracted by a single, nonblinded reviewer.

Data Analysis

For infarct volume and neurobehavioral score, we calculated a normalized mean difference effect size for each comparison and combined these in a weighted mean difference meta-analysis using a random-effects model. Where different measures of neurobehavioral outcome were reported from the same cohort of animals for the same time point, we combined these (prenested) comparisons using fixed-effects meta-analysis (nesting) and used this summary estimate in the random-effects model. For neurogenesis, we grouped the individual outcome measures and calculated an overall standardized mean difference effect size.

We used metaregression to examine the impact of (1) biological factors (eg, time, dose, and route of drug administration, time of assessment of outcome), (2) aspects of study design (eg, type of antidepressant drug, anesthesia, species of animal, the presence of comorbidities), and (3) elements of study quality (eg, whether animals were randomized to groups and blinded induction of ischemia and assessment of outcome were performed). We conducted subgroup analyses limited to SSRIs. We used the metareg function of STATA/SE11 to conduct univariate metaregression with a significance level set at P<0.05. We calculated adjusted R² values (a measure of how much heterogeneity is explained by the model) to estimate the proportion of the variability in reported effect sizes which might be explained by variation in the independent variable in question.

We assessed for the presence of publication bias using funnel plotting, Egger regression, and trim and fill. Results are presented as the percentage improvement in outcome and its 95% confidence intervals (CIs). For data presented as line graphs, the size of the circles represents the precision of each study (inverse of within-study variance), For data presented as bar graphs,
the width of each bar is the log of the number of animals in that subgroup, vertical error bars represent the 95% CI for the individual estimates, and the horizontal gray bars represent the 95% CI of the pooled estimate of efficacy.

Results

We identified 2016 publications, of which 648 were duplicates, giving 1368 unique publications. Screening title and abstracts gave 138 publications that were potentially relevant and for which we retrieved the full text. Of these, 94 publications were excluded because, for example, they had no relevant control group, did not have applicable outcome measures, or were missing key data. Forty-four publications were included in the analysis (Figure I in the online-only Data Supplement).

Twenty-two different antidepressant drugs were used in the included studies; these were categorized into 10 subtypes (Table I in the online-only Data Supplement).

Two studies reported the use of environmental enrichment, and 1 study provided rehabilitation poststroke, in addition to antidepressant treatment. Eleven studies used mice, 32 used rats, and 1 study reported the use of both rats and mice. One study used hypertensive animals, another used aged animals, 8 studies modeled CMS in the animals, and the remaining 34 studies did not model a relevant comorbidity. The time at which drugs were delivered was not reported in 7% of the experiments. Twenty-nine percent of all experiments administered drugs before, or at the same time as, the induction of ischemic injury; 46% delivered drug between 30 minutes and 48 hours and 16% initiated treatment after 7 days (Table II in the online-only Data Supplement).

The median number of quality checklist items scored was 5 of a possible 10 (interquartile range, 4–7). No studies reported a sample size calculation, and all were peer reviewed. More than half of the studies reported random allocation to treatment groups (55%) and blinded assessment of outcome (61%), whereas just more than a third reported allocation concealment (34%; Table III in the online-only Data Supplement).

Effect of Antidepressant Treatment on Infarct Volume

Infarct volume after antidepressant treatment was reported in 29 publications, with 60 experiments nested into 58 comparisons, using 683 animals (Figure 1A). Twelve different antidepressants were used, and taken together, these reduced infarct volume by 27.3% (95% CI, 20.7%–33.8%), with substantial heterogeneity in the estimates ($I^2=74.3\%$). First drug administration occurred from 21 days before stroke induction to 8 days postinduction. We did not observe any evidence of publication bias using funnel plot, Egger regression, or trim and fill (data not shown). There was an inverse relationship between the number of quality checklist items scored and reported effect size (adjusted $R^2=5.1\%; P<0.027$), with higher quality studies giving lower estimates of efficacy (Figure 1B).

Efficacy was 24% lower in the 28% of experiments (193/683 animals) that reported concealment of treatment group allocation during the induction of ischemia (adjusted $R^2=20.2\%, P<0.005$; Figure 1C). There was no effect of drug subtype,
individual drug, whether drug administration occurred pre- or postinsult, blinded assessment of outcome, random allocation to group, control of temperature, compliance with animal welfare regulations, statement of potential conflict of interest, use of comorbid animals, or use of anesthetic without marked neuroprotective properties (data not shown).

**Effect of Antidepressant Treatment on Neurobehavioral Score**

Effects on neurobehavioral score were reported in 33 publications describing 154 experiments nested into 98 comparisons, involving 1319 animals (Figure 2A). Thirty-six individual neurobehavioral tests were identified, and we categorized these as those that assessed memory or learning outcomes, motor or sensory outcomes, or behaviors relevant to depression (Table IV in the online-only Data Supplement). Eighteen different antidepressants were used, and the time of first administration ranged from 17 days prestroke to 35 days poststroke. There was an overall improvement in neurobehavioral score of 53.7% (46.4%–61.1%), again with substantial heterogeneity ($I^2=85.1\%$). We observed funnel plot asymmetry, confirmed with Egger regression, and trim and fill analysis suggested 29 theoretical missing studies with a corrected improvement in neurobehavioral score of 36.5% (28.7%–44.3%), suggesting a 47.1% relative overestimation in treatment effect (17.2% [9.9%–24.6%] absolute overestimation of efficacy; Figure 2B, 2C and 2D).

Six study characteristics contributed to different estimates of efficacy. Drug subtype (adjusted $R^2=32.9\%; P<0.0001$; Figure 3A) and individual drug (adjusted $R^2=41.6\%; P<0.0001$; Figure 3B) were significant sources of heterogeneity. Larger effects were observed in neurobehavioral tests assessing memory and learning or depressive behaviors than in those measuring motor or sensory function (adjusted $R^2=25.7\%; P<0.0001$; Figure 3C). Efficacy was 82.3% higher (76.0% versus 41.7%; 95% CI for difference, 32.7%–132.0%) for studies assessing memory or learning compared with those assessing motor or sensory function and 80.7% higher (75.3% versus 41.7% [40.3%–121.0%]) for studies assessing behaviors relevant to depression (Figure 3C).

Sixty-four percent (841/1319) of the animals used to assess changes in neurobehavioral outcome were randomly allocated to treatment group. The 458 animals in which CMS was modeled (35%) were all randomized. Treatment effects were larger in studies that reported random allocation of animals to treatment group (adjusted $R^2=16.3\%; P<0.001$; Figure 4A) in studies that used an anesthetic with marked intrinsic neuroprotective properties (adjusted $R^2=7.1\%; P<0.05$; Figure 4B) and where the animals used had a comorbidity (adjusted $R^2=26.9\%; P<0.0001$; Figure 4C) and were 40% smaller in studies that reported control of body temperature during...
the induction of ischemia (adjusted $R^2=37.4\%$; $P<0.0001$; Figure 4D). Whether drug administration occurred pre- or postinsult, aggregate quality score, blinded assessment of outcome and induction of ischemia, compliance with animal welfare regulations, and statement of potential conflict of interest did not contribute to the detected heterogeneity (data not shown).

**Effect of SSRI Treatment on Infarct Volume**

SSRI treatment reduced infarct volume by 26.9% (13.2%–40.7%), with substantial heterogeneity ($I^2=77.5\%$) in 23 comparisons involving 176 animals. SSRIs were first administered from 7 days before to 8 days after stroke induction. We observed an inverse relationship between the number of quality checklist items scored and reported efficacy (adjusted $R^2=39.4\%$; $P<0.009$; Figure 5A). Each study that reported allocation concealment during the induction of ischemia also reported random allocation to group, so the impact of these factors cannot be separately defined. These studies reported smaller treatment effects (adjusted $R^2=27.0\%$; $P<0.047$; Figure 5B).

We also observed collinearity between the route of drug delivery and the dosing procedure meaning that it is not possible to distinguish between the impacts of each. All multiple dosing regimens used intraperitoneal delivery, one study gave a continuous infusion subcutaneously and 70% of studies gave drug as a single intravenous dose; efficacy was higher in these circumstances than with other approaches to dosage and delivery (adjusted $R^2=30.7\%$; $P<0.0453$; Figure 5C).

Time of assessment and drug administration, whether drug administration occurred pre- or postinsult, individual SSRI used, anesthetic, species, strain, type of ischemia, and type of comorbidity did not contribute significantly to the observed heterogeneity (data not shown).

**Effect of SSRI Treatment on Neurobehavioral Score**

Neurobehavioral outcome following SSRI treatment was reported in 36 comparisons using 445 animals; 31 individual neurobehavioral tests were identified and categorized (Table IV in the online-only Data Supplement). Neurobehavior improved by 51.8% (38.6%–64.9%), and again, heterogeneity

Figure 3. Effect of antidepressant treatment on neurobehavioral scores (NBSs). Effect of (A) drug subtype, (B) individual antidepressant drug, and (C) the type of behavior being assessed by the test on the improvement in NBS.
was high ($I^2=85.6\%$). First drug administration occurred from 7 days prestroke to 35 days poststroke.

Longer durations between ischemia and the time of outcome assessment were associated with greater treatment effects (adjusted $R^2=38.8\%$; $P<0.002$; Figure 6A). The route of drug delivery (adjusted $R^2=29.7\%$; $P<0.0156$; Figure 6B) and dosing procedure (adjusted $R^2=29.8\%$; $P<0.008$; Figure 6C) also accounted for between-study heterogeneity.

Figure 4. Effect of antidepressant treatment on neurobehavioral scores (NBSs). Effect of (A) randomly allocating animals to a group, (B) use of an anesthetic without marked intrinsic neuroprotective properties during stroke induction, (C) use of comorbid animals, and (D) control of temperature during induction of stroke on the improvement in NBS.

Figure 5. Effect of selective serotonin reuptake inhibitor (SSRI) treatment on infarct volume. (A) Metaregression of reduction in infarct volume vs overall quality scores. (B) Effect of randomly allocating animals to a group and blinding the induction of ischemia (collinear variables) on infarct volume. (C) Effect of SSRI administration route and dosing procedure (collinear variables) on infarct volume.
The largest effects were seen in studies that did not report the anesthetic agent used (compared with those that did report the anesthetic used; adjusted $R^2=41.9\%$; $P<0.003$; Figure 6D), studies that reported random allocation to group (adjusted $R^2=18.0\%$; $P<0.041$; Figure IIA in the online-only Data Supplement), and studies that used mice rather than rats (adjusted $R^2=12.9\%$; $P<0.019$; Figure IIB in the online-only Data Supplement). Treatment effects were smaller in studies that reported control of animal body temperature during the induction of ischemia (adjusted $R^2=32.6\%$; $P<0.002$; Figure IIC in the online-only Data Supplement), or the use of anesthetics without marked neuroprotective properties (adjusted $R^2=20.1\%$; $P<0.012$; Figure IID in the online-only Data Supplement). Treatment effects were larger in studies that provided a statement of potential conflict of interest (adjusted $R^2=20.1\%; P<0.012$; Figure IIE in the online-only Data Supplement).

The quality score, blinded assessment of outcome and induction of ischemia, compliance with animal welfare regulations, use of comorbid animals, time of drug administration, whether drug administration occurred pre- or postinsult, drug used, strain of animal, type of ischemia, test type, and type of comorbidity did not significantly contribute to model variance (data not shown).

Efficacy was not significantly different in 13 comparisons using CMS compared with 23 comparisons that did not, and therefore, subanalysis of the effects of SSRI treatment within each of these groups was not performed. At the request of a reviewer, we performed a post hoc test of the effect of CMS on neurobehavioral score across all drugs (ie, not limited to SSRIs). We had not done this previously because we were concerned that substantial heterogeneity in the overall data set would limit the usefulness of this analysis. Studies that used CMS reported larger improvements in neurobehavior (74.4% [60.8%–88.2%]) compared with those that did not (41.7% [33.7%–49.7%]; adjusted $R^2=26.9\%$; $P<0.001$). We then calculated an effect size for the difference in neurobehavioral improvement in CMS versus non-CMS studies and found that efficacy was 78.7% (95% CI for difference, 43.4%–113.9%) higher. When restricted to studies using SSRIs, this difference was 58.8% (−9.5% to 127.1%). Given the overlap in these CIs, we think it is likely that SSRIs are indeed more effective in animals exposed to CMS, but given the post hoc nature of the analysis and the lack of statistical significance, this finding can be considered as hypothesis generating only.

**Effect of Antidepressant Treatment on Neurogenesis**

Effects on measures of neurogenesis were reported in 5 publications describing 16 experiments nested into 10 comparisons involving 113 animals. All 5 publications reported differentiation and proliferation of new neurons as outcome measures, 3 reported cell survival, and 1 reported cell migration. Citalopram treatment was examined in 6 nested comparisons, and fluoxetine treatment was examined in 4. Overall, there was an improvement in neurogenesis outcome measures of 2.2 SD (1.3–3.0). There were too few studies to perform subgroup stratification, and these data were not analyzed further.

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**Figure 6.** Effect of selective serotonin reuptake inhibitor (SSRI) treatment on neurobehavioral scores (NBS). A, Metaregression of improvement in NBS vs time of outcome assessment. Effect of (B) SSRI administration route and (C) dosing procedure and (D) type of anesthetic used during stroke induction on the improvement in NBS.
Discussion

This study assesses the preclinical literature reporting administration of antidepressants for the treatment of ischemic stroke. Investigation into the effects of antidepressants on poststroke depression and on cognitive and functional outcome in both depressed and nondepressed subjects are ongoing in preclinical and clinical research. Eight of the 44 studies included in the current analysis modeled depression using the CMS paradigm. The data indicate improvements in structural and functional outcomes after antidepressant administration in animal models of ischemic stroke both with and without CMS, regardless of the time of drug administration. This supports the case for further clinical trials of antidepressants for both depression and neurological recovery.

Overall, antidepressant treatment reduced infarct volume. However, consistent with previous findings, studies that received a higher aggregate quality score reported smaller infarct volume reductions.24,25 Studies that blinded induction of ischemia reported no effect of antidepressant treatment on infarct volume, indicating these data are at high risk of bias. The type of drug and drug subtype had no effect on heterogeneity, suggesting different mechanisms of action did not influence the ability of antidepressant drugs to reduce lesion volume.

Evidence of publication bias suggests an overstatement of efficacy in neurobehavioral outcomes. Nonetheless, a considerable improvement of 36.5% remained after theoretically missing studies were included using trim and fill. The largest and most precise data set was that examining the effect of SSRIs, and studies investigating newer drugs such as herbal extracts and the neurokinin 1 (NK1) tachykinin receptor antagonist, N-acetyl-L-tryptophan, also reported substantial improvements in neurobehavioral scores. The monoamine oxidase inhibitors did not improve neurobehavioral outcome. However, data for these interventions were limited and highly variable.

Tests assessing depressive behaviors or memory and learning resulted in larger effect sizes than those testing motor or sensory function. This indicates a greater effect of antidepressants through traditional, mood-regulating mechanisms of action; however, effects on motor and sensory outcomes were also robust, supporting the results of clinical trials assessing motor outcome with antidepressant treatment after stroke.3,10,26 Effects of treatment were also greater in comorbid animals, reflecting the fact that the main comorbidity, CMS, is used to induce depressive behaviors in rodents, and therefore, tests for these behaviors were primarily performed in these studies. In contrast to previous findings, randomization to group was associated with a larger improvement in behavior. This could be attributable to the confounding effects of other variables: all studies that reported use of CMS also randomized animals to group. Fluoxetine was the most commonly studied SSRI; however, there was no detectable impact of the type of SSRI on structural or functional outcomes.

The largest effects on neurobehavior were seen with multiple doses of oral antidepressant administration, confirming maximum efficacy in the most clinically relevant administration procedure. Benefit with SSRI treatment was conserved across studies that used CMS to model depression and those that did not, supporting the use of SSRIs in both depressed and nondepressed patients with stroke.

Time of SSRI administration had no impact on neurobehavioral improvement, and analysis of pre-versus postinsult administration of all antidepressants and SSRIs also revealed no impact of treatment time on neurobehavioral or infarct outcomes. Included studies reported first administration from >2 weeks prestroke to >1 month poststroke, indicating benefit of even late treatment. Importantly, effect sizes were larger when behavior was assessed at later time points. These results support an effect of SSRIs on behavior independent of tissue salvage, indicating a potential role in regeneration and repair rather than acute neuroprotective effects.

SSRIs may have effects on structural adaptation after ischemic damage, including modulation of neuroplasticity and neurogenesis.1-9 We identified only 5 publications reporting the effect of SSRIs on neurogenesis, and although improvement in these measures was observed after treatment, too few comparisons were identified for more detailed analysis.

As with most animal stroke research, the included studies are largely restricted to healthy, young male rodents, limiting the external validity of results. In addition, only 1 study reported physical therapy and 2 reported environmental enrichment meaning that the effects of physical stimulation on recovery could not be assessed. Clinical reports suggest a facilitatory effect of pharmacological therapy on rehabilitation.30,31 In this analysis, we cannot distinguish the effects of cotreatments such as environmental enrichment and physical therapy from the effects of antidepressant treatment. However, only 3 of 44 included studies reported the use of these rehabilitative techniques, and sensitivity analysis shows that excluding these studies does not affect the results presented.

No studies reported a sample size calculation, consistent with the low reporting of this factor in previous stroke and other neurological disease analyses.24,28,29

Further limitations include that only the final neurobehavioral scores reported by a study were extracted. If a treatment increased the speed of recovery, this was not captured by the current analysis. The collinearity of certain data detailing the effect of SSRI treatment on infarct volume means that we are unable to distinguish between the impacts of the variables in question. Additionally, the limited data available means that investigation of individual drug biology was not possible.

Conclusions

Some antidepressants improve infarct volume and neurobehavioral scores in animal models of focal ischemic stroke. Infarct volume outcomes seemed to be at particular risk of bias, limiting the internal validity of these data and suggesting caution when interpreting results. Neurobehavioral outcomes.
were more robust and potentially more relevant given the probable action of antidepressants on regenerative processes rather than acute neuroprotection. However, the lack of clear mechanistic insight into antidepressant efficacy is an avenue that requires further investigation.

Despite limitations, the animal data are in line with the available clinical data, supporting the use of inferences made through animal models for assessing the impact of antidepressant treatment. Both preclinical and clinical data suggest a role for antidepressants to facilitate recovery of function, independent of an effect on mood.

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