The clinical use of drugs influencing neurotransmitters in the brain to promote motor recovery after stroke; a Cochrane systematic review

H. I. BERENDS1, J. M. M. NIJLANT1,2, K. L. L. MOVIG3, M. J. A. M. VAN PUTTEN4, M. J. A. JANNINK1, M. J. IJZERMAN5

The objective of this review was to compare and to discuss the results of studies that investigated the ability of drugs to improve motor recovery after stroke by influencing dopamine, norepinephrine, or serotonin concentrations in the brain. A systematic literature search up to January 2009 was conducted in MEDLINE, Pubmed, EMBASE and in the database of the Cochrane Stroke Group Trial Register. In addition, the literature reference lists of the relevant publications were checked. The literature search was conducted in order to identify randomized controlled trials focusing on the effects of drugs on motor recovery after stroke. In order to structure the data, motor recovery was subdivided into motor control and motor function. The methodological quality of the studies was also assessed. Six studies, investigating the effects of 7 different kinds of drugs were included. Methodological scores varied between 10 and 14 (max 19). Motor control was not influenced by any of the drugs. Motor function improved in patients treated with methylphenidate, trazodone, and nortriptyline. Results for fluoxetine and levodopa were contradicting. There is insufficient evidence to conclude that neuromodulating drugs targeting serotonin, norepinephrine, or dopamine influence motor recovery after stroke.

KEY WORDS: Stroke - Neurotransmitter agents - Recovery of functions.

A stroke or a cerebrovascular accident (CVA) is a sudden ischemic or hemorrhagic disturbance in the blood supply to the brain that results in complete or partial loss of brain function. In industrialized countries, it is the leading cause of disability, and one of the major consequences of a disturbed co-ordination of (fine) motor tasks. Therefore, the (re)learning of motor function plays an important role in the rehabilitation after a stroke. After the initial recovery, cortical plasticity is presumed to be important for the improvement of motor function. Cortical plasticity is established by several mechanisms, including unmasking of silent synapses, sprouting of nonaffected fibers, regeneration of axons, and long-term potentiation (LTP). Unmasking of previously silent synapses is promoted by an increased excitability of the brain. In sprouting, new synapses are formed and in LTP an increase in synaptic strength provides more stable changes in the horizontal connections within the primary motor cortex.

The release of local neurotransmitters (acetylcholine, noradrenalin, serotonin, dopamine, and histamine) is thought to influence cortical plasticity, since an
increased amount of these neurotransmitters enhances the excitatory input of glutamate in cortical neurons. This enhanced input of glutamate in turn facilitates N-methyl-D-aspartate (NMDA) receptor activation. When intracellular events following NMDA receptor activation overcome a threshold, synaptic modifications occur. The facilitation of NMDA receptor activation might therefore promote these synaptic modifications, which are important in cortical plasticity. Previous studies have found a relation between these neurological changes and motor control and functional abilities. Therefore, it is hypothesized that drugs that increase the amount of neurotransmitters, will facilitate cortical plasticity, and thereby also motor recovery after stroke.

Several drugs influence the amounts of neurotransmitters in the brain. Dextro- and methamphetamine are examples of drugs that increase the amounts of dopamine, norepinephrine, and serotonin in the synaptic cleft by inhibiting the re-uptake of these neurotransmitters into the presynaptic terminal. Studies investigating the effects of these amphetamines on motor recovery after stroke have been extensively summarized in a previous review. This review suggested that motor and language function might improve with amphetamine-treatment. However, no effect of treatment on activities of daily living, neurological function, or depression was found. Other studies on amphetamines show insufficient evidence of a facilitating effect of dextroamphetamines on motor function. Because of these previously published data, amphetamines are not taken into account in the present review. Recently, Rösser and Floël published a descriptive overview of the conclusions of studies examining pharmacological enhancements of motor recovery after stroke. This study concluded that preliminary data are promising, and larger clinical trials are needed. However, this review only considered the conclusions of the studies and did not take the quality into account. To come to a deeper understanding of the way of action of the pharmacology and the relation with motor recovery, the present review systematically analyzes the results of studies examining pharmacological treatment in stroke aimed to improve motor function.

Several drugs have a rather selective influence on neurotransmitters in the brain. Levodopa (L-dopa), increases dopamine concentrations in the brain. It is the metabolic precursor of dopamine, and it is able to cross the blood-brain barrier. In the brain it is converted into dopamine. Methylphenidate also increases the amount of dopamine in the brain by blocking the re-uptake of dopamine (and also norepinephrine) into the presynaptic neurons and by increasing the release of these neurotransmitters into the extraneuronal space. Dopamine is a neurotransmitter that most likely regulates plasticity in neuronal circuits, and it reduces or facilitates communication among neurons. Dopamine is involved in the regulation of motor control and the learning of motor programs and habits. It is also required for voluntary movement.

Antidepressants, such as desipramine, maprotiline, and nortriptyline are drugs that predominantly influence the amount of norepinephrine in the brain. Desipramine is a tricyclic antidepressant, and it is suggested that it increases norepinephrine amounts by blocking the reuptake from the synapses in the central nervous system. Maprotiline is an antidepressant which non-selectively inhibits monoamine re-uptake, resulting in an inhibition of re-uptake of norepinephrine in the presynaptic neurons. Nortriptyline also blocks the uptake of norepinephrine in the presynaptic neurons. Norepinephrine is the predominant transmitter in the autonomic nervous system, and plays an important role in learning and memory.

Fluoxetine and trazodone are drugs that influence the amount of serotonin in the brain. Fluoxetine is a selective serotonin re-uptake inhibitor which increase serotonin amounts in the synaptic cleft by inhibiting the reuptake of serotonin by the presynaptic neuron. Besides its effect on serotonin-receptors, Trazodone also affects histamine, and α1 adrenoreceptors and possibly inhibits the action of recombinant T-type channels. Serotonin is thought to facilitate motor output. It has also been hypothesized that serotonergic neurons play an auxiliary role in coordinating appropriate autonomic and neuroendocrine outputs to the ongoing tonic or repetitive motor activity.

The objective of this research is to systematically review the results of studies that investigated the ability of drugs to improve motor recovery by influencing dopamine, norepinephrine, or serotonin concentrations in the brain.

Methods

Literature search

A systematic literature search up to January 2009 was conducted in MEDLINE, Pubmed, EMBASE and
### Table I. — Fifty-five Patients With Elevated TgAb levels (>100 IU/mL) during follow-up for DTC.

<table>
<thead>
<tr>
<th>Stroke</th>
<th>PT Measures</th>
<th>Medication (duration)</th>
<th>N</th>
<th>Age (years)</th>
<th>Time after stroke</th>
<th>Motor function prior to therapy</th>
<th>Motor function after therapy</th>
<th>Side-effects and drop-out</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dam et al.</strong>&lt;sup&gt;15&lt;/sup&gt; Middle cerebral artery</td>
<td>Yes</td>
<td>HSS, HSSmotor, HSSgait, Bi</td>
<td>14</td>
<td>68.1±7.7</td>
<td>2.9±1.7 months</td>
<td>BI: 36.4±17.8 HSS: 54.4±12.7 HSSmotor: 35.4 ±4.8 HSSgait: 5.7±0.7</td>
<td>BI: 47.9±15.5 HSS: 32.2±4.7 HSSmotor: 32.2 ±4.7 HSSgait: 4.8± 1.5</td>
<td>2: move to other rehabilitation center 1: epileptic seizures 2: sedation (for several days) (continued the study)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maprotiline 150mg (3 months)</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Fluoxetine 20mg (3 months)</td>
<td>16</td>
<td>67.5±8.9</td>
<td>2.7±1.8 months</td>
<td>BI: 38.4±11.2 HSS: 49.4±9.8 HSSmotor: 35.4 ±3.9HSSgait: 5.9±0.5</td>
<td>BI: 61.9±13.0 HSS: 32.4±3.8 HSSmotor: 32.4 ±3.8 HSSgait: 3.8±0.9</td>
<td>2: epileptic seizures 2: transient nausea or insomnia (continued the study)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (3 months)</td>
<td>16</td>
<td>68.4±5.5</td>
<td>3.1±1.9 months</td>
<td>BI: 35.0±10.8 HSS: 35.5±4.8 HSSmotor: 35.5 ±4.8 HSSgait: 5.8±0.4</td>
<td>BI: 54.1±21.1 HSS: 31.6±5.0 HSSmotor: 31.6 ±5.0 HSSgait: 4.6±1.3</td>
<td>1: second stroke</td>
<td></td>
</tr>
<tr>
<td><strong>Grade et al.</strong>&lt;sup&gt;16&lt;/sup&gt; Inpatients</td>
<td>Yes</td>
<td>FM FIM</td>
<td>10</td>
<td>69.8±3.66</td>
<td>17.9±3 days</td>
<td>FM: 34.5±12.8 FIM: 97.0±5.8</td>
<td>FM: 55.3±7.1 FIM: 116.5±3.6</td>
<td>4: early discharge 1: abdominal pain from peptic ulcer disease</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylphenidate 5-30mg (3 weeks)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (3 weeks)</td>
<td>11</td>
<td>72.6±3.49</td>
<td>18.7±3.57 days</td>
<td>FM: 29.8±9.1 FIM: 90.8±5.6</td>
<td>FM: 37.8±5.0 FIM: 104.9±3.4</td>
<td>2: early discharge 1: worsening depression</td>
<td></td>
</tr>
<tr>
<td><strong>Miyai et al.</strong>&lt;sup&gt;19&lt;/sup&gt; Inpatients</td>
<td>Yes</td>
<td>FM FIM</td>
<td>5</td>
<td>76 ±7</td>
<td>34±8 days</td>
<td>FM: 67±20 FIM: 114±21</td>
<td>FM: 82±25 FIM: 122±26</td>
<td>1: development of glaucoma</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluoxetine (4 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desipramine (4 weeks)</td>
<td>12</td>
<td>73±13</td>
<td>40±7 days</td>
<td>FM: 51±16 FIM: 116±30</td>
<td>FM: 51±15 FIM: 114±52</td>
<td>2: confusion 1: orthostatic hypotension 1: tachycardia 1: possible drug rash</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trazodone (4 weeks)</td>
<td>6</td>
<td>73 ±5</td>
<td>42±5 days</td>
<td>FM: 56±19 FIM: 122±34</td>
<td>FM: 72±23 FIM: 130±39</td>
<td>1: died due to pulmonary embolus 1: medical deterioration 2: refused treatment</td>
<td>—</td>
</tr>
<tr>
<td><strong>Robinson et al.</strong>&lt;sup&gt;21&lt;/sup&gt;-Depressed Stroke</td>
<td>No</td>
<td>JHFI FIM</td>
<td>23</td>
<td>65±14</td>
<td>16±35 Weeks</td>
<td>JHFI: 4.6±4.3 FIM: 58.3±13.1</td>
<td>JHFI: 3.2±4.3 FIM: 59.2±11.6</td>
<td>3: gastrointestinal symptoms 6: refused treatment</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fluoxetine 10-40mg (12 weeks)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nortriptyline 25-100mg (12 weeks)</td>
<td>16</td>
<td>64±10</td>
<td>5±4 Weeks</td>
<td>JHFI: 6.6±6.1 FIM: 52.0±16.8</td>
<td>JHFI: 3.5±3.0 FIM: 60.5±12.2</td>
<td>2: medical deterioration 1: refused treatment</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo (12 weeks)</td>
<td>17</td>
<td>73 ±8</td>
<td>6±3 Weeks</td>
<td>JHFI: 7.8±2.6 FIM: 48.9±6.7</td>
<td>JHFI: 4.1±2.7 FIM: 56.2±7.8</td>
<td>1: medical deterioration 2: refused treatment</td>
<td>—</td>
</tr>
</tbody>
</table>

(Continued)
in the database of the Cochrane Stroke Group Trial Register. The following key words were used in these searches: cerebrovascular disorders, rehabilitation, activities of daily living, treatment outcome, motor skills, motor activity, movement, pharmacology, neurotransmitter uptake inhibitors, and neurotransmitter agents. The Pubmed search is described in Appendix 1 and was adapted to suit the other databases. In addition, the literature reference lists of the relevant publications were carefully checked.
Selection criteria

Studies that met the following criteria were included: 1) completed, randomized, controlled, published clinical trials in humans; 2) the drug tested had to affect dopamine, norepinephrine, or serotonin amounts in the brain; 3) the primary outcome measure had to be related to motor recovery after stroke, studies only measuring with the Barthel Index, or the Rankin score were excluded; 4) the drug had to be administered during a prolonged period of at least 2 weeks; 5) full-length publication in English, German, or Dutch. Case reports were not included.

Assessment of methodological quality

To evaluate the methodological quality of the studies, we used the “Criteria List for the Methodologic Quality Assessment” of Van Tulder.24 This list consists of internal validity criteria, descriptive criteria, and statistical criteria, assessed by 19 questions which could be answered with “Yes”, “No”, or “Don’t know” (Appendix 2). Each positive answer scored 1 point and each negative, or unclear answer scored 0 points. Each trial was evaluated by three reviewers independently (HB, JN, MIJ), and any disagreement between the reviewers was cross-checked and solved by discussion.

Data-extraction and analysis

In order to analyze the contents of the selected studies, study characteristics were extracted from the manuscripts (Table I). This information includes:

— the methodological quality of the study;
— the intervention(s) used in the study;
— the descriptive features of the subjects (age, time since stroke, kind of stroke);
— the number of included patients;
— the motor scores prior to the intervention and the motor scores after intervention;
— the side-effects and drop-out;
— decrease or increase of depression during study period.

In defining the clinical outcome (motor recovery) we separated motor control from motor function. Motor control is defined as the ability to use the muscles in order to accomplish a task, and can be measured (among other methods) with the Fugl-Meyer motor assessment (FM). On the other hand, motor function is defined as the ability to function in daily life, which can be measured (among other methods) with the Barthel Index (BI), the motor section of the Hemispheric Stroke Scale (HSSmotor), the Functional Independence Measure (FIM), Rivermead Motor Assessment (RMA), and the Johns Hopkins Functioning Inventory (JHFI). When interpreting the data we used these categories.

The differences in the changes in motor control and motor function before and after the intervention between the medication and placebo groups were considered to be significant if P<0.05.

In the assessment of the drugs, the safety and the possible side-effects of the drug were taken into account.

Results

Four publications 14, 15, 19, 20 fulfilled all the selection criteria (Appendix 1) and were included in the review. Two more articles were retrieved via the reference lists.16, 21 The studies that are included are summarized in Table I.

In 6 studies, 7 different kinds of drugs were tested in 266 patients with 6 different outcome measures. In order to make a comparison despite the large number of variables, the outcome measures were grouped into measures of motor function or motor control. All studies investigated the motor function with the HSSmotor, BI, FIM, RMA, or JHFI. Motor control was measured in only three studies with the FM.15, 16, 19

Dam et al.20 found a significant improvement in motor function in all groups over time. However, according to the BI, motor function improved significantly more in patients treated with fluoxetine than in patients treated with maprotiline. The HSSmotor score found no significant differences between groups, but the HSS gait scores did. Motor control was not measured. No significant differences were found between any of the treatment groups and the placebo group.

Grade et al.16 found that patients treated with methylphenidate had a better recovery of motor function (FIM), compared to the placebo groups, with no effect on motor control (FM). In this study, the patients receiving methylphenidate showed a decreased degree of depression, compared to the study group receiving placebo.

Scheidtmann et al.14 found that patients receiving levodopa had significantly more improvement in
motor function (RMA) than those receiving placebo. This improvement was maintained, or increased even further in both groups for at least 3 weeks after the end of the treatment. In this study, depression was not measured. However, levodopa is not an antidepressant.

Miyai et al.\textsuperscript{19} found that motor function improved more in patients who were treated with trazodone and fluoxetine than in patients treated with desipramine (FIM). The differences in motor function were mainly due to sub-scores for ADL and mobility, and not cognition sub-scores. There were no significant differences in improvement in motor control (FM). All three of the drugs that were tested were found to have the same effect on depression.

Robinson et al.\textsuperscript{21} studied the effects of fluoxetine, nortriptyline and placebo on motor function in depressed and non-depressed patients separately. In the group of depressed patients, contradicting results were found between two motor function scales. According to the BI, they found a significantly greater improvement in motor function in patients who were treated with nortriptyline or placebo than in patients who were treated with fluoxetine. The JHFI scores did not differ between the treatments in the depressed patient group. The patients treated with nortriptyline had a significantly greater decline in Hamilton Rating Scale for Depression (HDRS) than the patients treated with placebo or fluoxetine. In the group of non-depressed patients, no differences in motor function or depression were found between the treatments.

Finally, Sonde et al.\textsuperscript{15} compared the effects of L-dopa alone, or in combination with amphetamines, with the effects of amphetamine alone and placebo. All patients improved significantly with regard to motor control (FM) and motor function (BI) over time. However, no additional increase was found in any of the treatment groups. The degree of depression was not measured.

The methodological scores are summarized in table 1. The scores vary between 10 and 14 out of 19, which led to the conclusion that the methodological quality of all the studies was moderate. The most conspicuous aspects are the lack of comparability between the groups at baseline with regard to the most important prognostic indicators, compliance therapy, and the lack of avoidance of co-interventions. Except for the study of Dam et al.,\textsuperscript{20} all studies had at least one important prognostic indicator that differed between the treatment groups. None of the studies described compliance with the therapy, and co-interventions were not described in three studies.\textsuperscript{15, 16, 21} In the study of Miyai et al.,\textsuperscript{19} co-interventions were not avoided. These aspects might have influenced the results of the studies.

Safety

Table I summarizes the described side-effects and the reasons for the drop-out. Because sub-acute stroke patients are susceptible for seizures, a second stroke, medical deterioration, and other medical problems, the drop-out rate in all of the studies was rather high. These reasons for drop-out were probably not due to the side-effects of the drug. However, in the treatment group receiving desipramine\textsuperscript{19} many of the reasons for drop-out (like drug rash, tachycardia or confusion) were probably due to side-effects of desipramine.

In several studies "refused treatment" is mentioned as a reason for drop-out. However, the reason for refusal is not mentioned, it could have been due to side-effects, but also to other variables influencing participation.

Discussion

In the present review 6 randomized controlled trials (RCTs) were found that assessed the effects of various drugs on motor recovery after stroke. To reduce the large number of variables, the outcome measures were sub-divided into measures of motor function and measures of motor control.

Motor control was not influenced by any of the drugs that were investigated in the studies. This is in contrast with the results of previous studies on the effects of a drug after a single dose in healthy subjects. In most of these studies, motor control improved after the intake of a single dose of fluoxetine,\textsuperscript{25} citalopram,\textsuperscript{26} or reboxetine \textsuperscript{27} in chronic stroke patients, and after the intake of fluvoxamine in healthy subjects.\textsuperscript{28, 29} However, one study found that a single levodopa dose was not sufficient to improve motor function in chronic stroke.\textsuperscript{30} In addition, we found no effect of a single dose of fluoxetine on motor function, or motor control, however, muscle activity during maximum voluntary force increased.\textsuperscript{31}

Neurological studies also suggest an influence of drugs on motor control. Pariente et al found an
increased activation in executive motor areas after fluoxetine intake in stroke patients. Loubinoux found a modulated activation in the sensorimotor area in healthy subjects after the intake of fluoxetine, fenozolone and paroxetine. The excitability of the sensorimotor cortex also increased after sertraline and fluoxetine intake in healthy subjects. In addition, two studies found a relationship between increased motor cortex excitability, decreased activation of the sensorimotor cortex and an improvement in the finger-tapping test score in healthy subjects.

Motor function improved in the patient groups treated with methylphenidate, trazodone, and nortriptyline. The results for fluoxetine and levodopa were contradicting. According to the hypothesis that the effects of drugs on motor function are established by mediation of neurotransmitter concentrations, it can be expected that drugs influencing the same neurotransmitters have the same effect on motor function. However, no relationship was found between the affected neurotransmitter and change in motor function, since the drugs that were found to facilitate motor function (methylphenidate, trazodone, and nortriptyline) did not differ from the drugs that were not found to improve motor function (maprotiline and desipramine). For example, maprotiline and nortriptyline both influence norepinephrine amounts. Nortriptyline was found to improve motor function, while maprotiline did not. In addition to the influence of the drugs on dopamine, norepinephrine, or serotonin concentrations, the drugs influencing norepinephrine concentrations, also influence adrenergic properties, since norepinephrine is a precursor of epinephrine. However, nor the results of drugs influencing epinephrine are consistent. The differences between the results of the studies might therefore not solely be explained by an increase in the different neurotransmitters in the brain.

Probably, other variables such as cognitive impairments or depression interfere with the effects of the drugs in stroke patients during long-term administration. We found no studies that investigated their influence on motor control. However, depression, neurological and cognitive factors are thought to influence the degree of motor function after a stroke. Of the included studies, only two measured the influence of the drug on the cognition of the patients (Mini Mental State Examination). Neither one of the studies found any reason to presume that cognitive factors influenced the outcomes.

However, changes in the degree of depression between the treatment groups did differ. Previous studies have shown that remission of depression was associated with a greater recovery of motor function. Also, in the studies included in the present review, an improvement in motor function in all treatments groups followed an improvement in the degree of depression. Although Hackett et al. found no definitive evidence that antidepressants prevent depression or improve recovery after stroke, the degree of depression might act as an effect-modifier, and it could be suggested that a drug improves the motor function by decreasing the degree of depression.

In addition to depression, several other differences between the treatment groups might have influenced the results. A variable that differs between treatment groups is the site of stroke, which might influence motor recovery and possibly also the effect of the drug. The study by Dam et al. is the only study that restricted the infarct location to a hemispheric middle cerebral artery. The other studies all included patients with a stroke in different areas of the brain. If patients with different sites of stroke are included, they should be equally distributed between the groups. However, in the study of Grade et al. twice as many patients with cortical stroke were included in the placebo group than in the group receiving methylphenidate treatment. Also in the study of Miyai et al. the site of stroke was not equally divided over the groups.

The interval between inclusion and stroke onset also differed between the groups. The degree of recovery depends largely on the time after the stroke - soon after a stroke the motor function is presumed to improve more than a few weeks or months after the stroke- therefore, it is important to balance the interval between inclusion and the stroke between the groups. Differences between these intervals make comparison between the studies hard. Sonde et al. included patients 5 to 10 days after a stroke, while Dam et al. included patients 3 months after stroke. Also, within some of the studies the interval between inclusion and the stroke differed between the treatment groups. In the study of Robinson et al. (depressed patient group) the mean time after the stroke in the fluoxetine group was 16±35 weeks, while the patients in the nortriptyline and placebo groups were included 5 ± 4 and 6 ± 3 weeks after the stroke, respectively. This could explain the differences found between the effects of fluoxetine, and nortriptyline and placebo.
Another difference between the groups is the degree of impairment at the start of the trial. In the studies of Miyai et al.,19 Robinson et al.21 (depressed patients), Scheidtmann et al.14 and Sonde et al.15, this motor impairment differed between the groups. When a group already has a high score for motor function, there is less potential to improve than in a group with a low initial score. The effect of the treatment can therefore not be compared between groups with different degrees of impairment.

The dosage of the drugs is also important when comparing studies. Loubinoux et al. indicated that differences between doses influence the outcome.33 The different results reported in the studies investigating fluoxetine might be due to this difference in dosage. None of the studies investigated the effects of different doses of the same drug.

The treatment of stroke patients with the drugs was found to be safe. However, the side-effects that did not result in drop-out were not described in three of the six studies. Only Dam et al.,20 Scheidtmann et al.,14 and Sonde et al.15 described all side-effects, including those that did not result in drop-out. Grade et al.16 only reported a rating of the seriousness of the side-effects. In addition, some studies were unclear in their description of the side-effects, since no reasons were given for refusal of treatment, or for medical deterioration. The description of all side-effects is important, because these can impede motor recovery.

In the decision to administer a drug, the side-effects have to be taken into account. However, if the inclusion and exclusion criteria are formulated with care, no drug needs to be omitted from future studies because of its side-effects.

Although a positive trend is found in the relation between administration of pharmacology and motor function, the hypothesis that an increased amount of any of the serotonin, norephinephrine, or dopamine neurotransmitters will improve motor recovery after stroke can be neither confirmed nor rejected.

To gain a better understanding of the effects of the drugs influencing the neurotransmitter concentrations in the brain and their influence on motor rehabilitation, more basic research has to be done. The mechanisms behind the effects of drugs are attributed to the influence on various neurotransmitters, which are presumed to be relevant in cortical plasticity. To evaluate their clinical utility, the effects of these drugs on cortical, spinal, and muscle activity have to be correlated with changes in motor function and motor control. When these processes are better characterized and understood we may ultimately recommend specific drug treatment in post-stroke patients to improve motor recovery during rehabilitation.

References


**APPENDIX 1**

Literature search, combination of keywords

#1 Cerebrovascular disorders [MeSH] OR Cerebrovascular accident[MeSH] OR Stroke[MeSH]

#2 Rehabilitation [MeSH] OR Rehabilitation [sub-heading] [MeSH] OR activities of daily living [MeSH] OR Treatment Outcome [MeSH]


#4 Pharmacology [MeSH] OR Pharmacology [sub-heading] [MeSH] OR Pharmacology, clinical

#5 Neurotransmitter uptake inhibitors [MeSH] OR Neurotransmitter Uptake inhibitors [pharmacological action] [MeSH] OR Dopamine Uptake Inhibitors [MeSH]

#6 Neurotransmitter Agents [MeSH] OR neurotransmitter agents [pharmacological action]

Limits were studies in Humans, English, German, Dutch

#1 AND #2 AND #3 AND #4

#1 AND #2 AND #3 AND #5

#1 AND #2 AND #3 AND #6

Appendix 2
## APPENDIX 2

“Criteria List for the Methodologic Quality Assessment” of Van Tulder\(^{24}\)

<table>
<thead>
<tr>
<th>Patient selection</th>
<th>A) Were eligibility criteria specified?</th>
<th>Yes/No/Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B) Treatment allocation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Was a method of randomization performed?</td>
<td>Yes/No/Don’t know</td>
</tr>
<tr>
<td></td>
<td>2. Was the treatment allocation concealed?</td>
<td>Yes/No/Don’t know</td>
</tr>
<tr>
<td></td>
<td>C) Were groups similar at baseline regarding the most important prognostic indicators?</td>
<td>Yes/No/Don’t know</td>
</tr>
<tr>
<td>Intervention</td>
<td>D) Were the index and control interventions explicitly described?</td>
<td>Yes/No/Don’t know</td>
</tr>
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<td></td>
<td>E) Was the care provider blinded to the intervention?</td>
<td>Yes/No/Don’t know</td>
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<td>F) Were co-interventions avoided or comparable?</td>
<td>Yes/No/Don’t know</td>
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<td>G) Was the compliance acceptable in all groups?</td>
<td>Yes/No/Don’t know</td>
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<td>H) Was the patient blinded to the intervention?</td>
<td>Yes/No/Don’t know</td>
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<tr>
<td>Outcome measurement</td>
<td>I) Was the outcome assessor blinded to the intervention?</td>
<td>Yes/No/Don’t know</td>
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<td></td>
<td>J) Were the outcome measures relevant?</td>
<td>Yes/No/Don’t know</td>
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<td></td>
<td>K) Were adverse effects described?</td>
<td>Yes/No/Don’t know</td>
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<td></td>
<td>L) Was the withdrawal/drop-out rate described and acceptable?</td>
<td>Yes/No/Don’t know</td>
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<td>M) Timing follow-up measurements</td>
<td></td>
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<tr>
<td></td>
<td>1. Was a short-term follow-up measurement performed?</td>
<td>Yes/No/Don’t know</td>
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<tr>
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<td>2. Was a long-term follow-up measurement performed?</td>
<td>Yes/No/Don’t know</td>
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<td>N) Was the timing of the outcome assessment in both groups comparable?</td>
<td>Yes/No/Don’t know</td>
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<tr>
<td>Statistics</td>
<td>O) Was the sample size for each group described?</td>
<td>Yes/No/Don’t know</td>
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<td>P) Did the analysis include an intention-to-treat analysis?</td>
<td>Yes/No/Don’t know</td>
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<td>Q) Were point estimates and measures of variability presented for the primary outcome measures?</td>
<td>Yes/No/Don’t know</td>
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