Supplementary Material

Pharmacological Treatment of Tremor in Parkinson's Disease Revisited

Supplementary Video 1. Classical upper limb parkinsonian resting tremor.

Supplementary Video 2. Cranial parkinsonian tremor involving lips, chin, jaw and buccinator muscles.

Supplementary Video 3. Re-emergent tremor in Parkinson's disease, setting in approximately 10 seconds after lifting the upper extremities.

Supplementary Video 4A. Patient with advanced Parkinson's disease showing marked bilateral resting tremor as well as re-emergent tremor in the OFF condition prior to his first levodopa morning dose.

Supplementary Video 4B. The same patient following treatment with his usual morning levodopa dose (150 mg) showing complete resolution of tremor and good mobility with very mild on period dyskinesias.

DRUGS TARGETING PD TREMOR: TRIAL SUMMARY

Levodopa

Although drug trials from the early levodopa era lack the methodological rigor of current placebo-controlled trials, levodopa proved superior to other antiparkinsonian agents available at the time (especially anticholinergics and amantadine) and levodopa is still regarded as the most efficacious oral drug for the treatment of motor symptoms of PD [1, 2]. The marked dose-dependent response of early PD to levodopa was confirmed by the randomized, double blind, placebo controlled ELLDOPA trial [3]. However, this study aimed at studying effects of levodopa on PD progression and patients with severe tremor were excluded. Few studies specifically addressed the effect of levodopa on PD tremor. An early randomized study of levodopa (without decarboxylase inhibitor) involving 56 mostly advanced stage PD patients found an average 66% improvement of tremor with long-term levodopa treatment, with 45 of

53 patients with tremor showing a mild to complete response [4]. Improvements of rigidity and bradykinesia were in a similar range (72 and 57%, respectively).

Koller compared the effect of levodopa, trihexiphenidyl and amantadine on tremor in a randomized, double-blind, short-term study [5]. Nine previously untreated, tremor-dominant hemiparkinsonian patients received each drug for 2 weeks. Fixed doses of levodopa/carbidopa (100/25 mg three times daily), trihexyphenidyl (2 mg four times a day) and amantadine hydrochloride (100 mg two times daily) were administered in random order, but it is unclear if there was a washout period between these treatments. Moreover, the doses of the drugs used in this study do not correspond to our current understanding of conversion factors [6], resulting in a relatively low dose of amantadine. Resting tremor was assessed using accelerometry. Tremor frequency was unchanged by treatment. Tremor amplitude was reduced by 55% with carbidopa/levodopa, 59% with trihexiphenidyl, and only 23% by amantadine. Individual responses to the different drugs were highly variable with some patients showing a marked tremor reduction on one drug but no improvement on other drugs and vice versa. Following the trial, five patients preferred trihexiphenidyl, four levodopa, and none preferred amantadine [5].

Tedeschi et al. examined the acute effect of levodopa on resting and postural tremor in a single-blinded, placebo-controlled, crossover study in 10 patients with stable levodopa response [7]. Finger tremor on the more severely affected side was measured using accelerometry 4 h after the last dose of medication and 45 min after taking 250/25 mg levodopa/carbidopa. Whereas placebo had no significant effect on tremor, levodopa reduced the power of resting and postural tremor by 48% and 42%, respectively without changing tremor frequency. Mean baseline tremor frequencies for resting and postural tremor in that study were 5.3 and 6.6 Hz, suggesting that the majority of the patients may have had re-emergent tremor [7].

Hughes et al. compared the acute effect of levodopa and sc. apomorphine on resting tremor [8]. The patients had fluctuations with severe off-tremor (12), stable disease with incapacitating tremor (5), or were untreated PD patients with conspicuous tremor (3). More than 12 h after their last dose of antiparkinsonian medication patients received a single dose of 250/25 mg levodopa/carbidopa and on a subsequent day sc. apomorphine at 1.5, 3.0, and 4.5 mg doses at 30 min intervals until tremor suppression or dose-limiting side effects occurred. Tremor was assessed using a custom-made 4-point tremor scale and the study was not blinded. Nineteen of 20 patients responded favorably to levodopa and apomorphine (mean dose 2.4 mg) with 10 patients showing complete resolution of resting tremor. Responses to

levodopa and apomorphine were equal in all patients [8]. In a similar open-label study, Kempster et al. compared the effect of levodopa and sc. apomorphine on various motor symptoms including tremor [9]. The study included 14 PD patients on chronic levodopa, the majority (12) with fluctuations. After withholding all anti-Parkinsonian medication overnight patients received a single dose of 250/25 mg levodopa/carbidopa and on a subsequent day sc. 1 to 4 mg (mean 2 mg) apomorphine. Tremor was assessed using a custom-made 4-point scale. Both drugs induced a similar magnitude and pattern of short-term motor responses including improvement of tremor [9].

Henderson et al. compared the effect of levodopa, propranolol, and placebo on resting and postural tremor, measured by accelerometry, in a small study [10]. Eleven levodopa-responsive patients, the half of whom suffered from fluctuations, were randomized to receive increasing single doses of either levodopa/benserazide (100/25, 200/50, and 300/75 mg), propranolol (20, 40, and 80 mg) or placebo in a blinded fashion. The other treatments were administered one and 2 weeks later in random order. Patients usually taking medication were asked to stop propranolol at least 1 week before entering the study. Levodopa was withheld for 12 h before intake of the study medication. Mean improvements in resting and postural tremor on the highest dose of levodopa were 70% and 61%, with 3 patients showing >95% reduction of both tremor types. On the highest dose of propranolol, four PD patients showed a >30% reduction of resting tremor amplitude, 3 patients a >30% amplitude reduction of postural tremor, but overall tremor response to propranolol was not significantly different from placebo [10].

A recent non-randomized, open-label study compared the effect of a single dose of levodopa/carbidopa with a dose of trihexiphenidyl [11]. Twenty subjects on a stable dose of levodopa, previously or presently taking trihexiphenidyl and without contraindications for anticholinergics were included. Patients had a mean age of 58 years and a disease duration of about 5 years. More than 12 h after their last dose of antiparkinsonian medication, patients received 4 mg trihexiphenidyl. Two days later patients received 200/50 mg levodopa/ carbidopa, also during a practically defined off. Improvement in UPDRS motor scores [12] and subscores for tremor, rigidity, bradykinesia, and axial symptoms served as outcomes. Levodopa led to a 60% improvement of the UPDRS motor score, and trihexiphenidyl to a 27% improvement of the motor score. Whereas the improvement of subscores for tremor, rigidity, bradykinesia, and axial symptoms was similar following levodopa (between 51% and 68% on average), trihexiphenidyl primarily improved tremor (UPDRS motor subscore items 20 und 21). Improvement of the tremor subscore was better on levodopa than on

trihexiphenidyl (approx. 67% vs. 46%). Eleven patients showed a better response of tremor to levodopa, 9 patients hat better improvement of tremor with trihexiphenidyl. Patients with better response to trihexiphenidyl showed lower baseline tremor scores [11], suggesting an overall stronger effect of levodopa on PD tremor.

Another study compared the effect of levodopa/benserazide on bradykinesia, rigidity, and tremor to differentiate between PD patients with dopamine-resistant vs. responsive tremor. Seventy-six patients received a single dose of 200/50 mg in the practically defined off state (≥12 h after the last dose of levodopa) [13]. Eligible patients had to show a visible resting tremor in at least one arm. Bradykinesia and rigidity had to be levodopa-responsive (≥20% improvement of the respective MDS UPDRS subscores).

On average, single dose levodopa led to a comparable improvement of bradykinesia (43%), rigidity (45%), and tremor (50%). Using cluster analysis, the authors could differentiate three clusters with good, intermediate, and poor response of tremor to levodopa. The difference in levodopa-response between those groups was somewhat smaller for bradykinesia and rigidity. However, it pointed in the same direction [13]. Importantly, baseline characteristics differed markedly between tremor-responsive, -resistant and intermediate patients. Those responsive to levodopa had longer disease duration and more severe motor impairment than tremor-resistant patients (mean 6.2 vs. 2.6 years, MDS UPDRS motor score off 52.6 vs. 37.2). In addition, responsive patients had a higher levodopa equivalent dose and a higher rate of dyskinesias than tremor-resistant patients (levodopa equivalent mean 510 vs. 406 mg, dyskinesias 52% vs. 10%), suggesting that these groups of patients were not fully comparable.

Finally, a post-hoc analysis of a randomized, placebo-controlled trial of levodopa (daily dose 300 mg) in 445 patients with early PD (LEAP-study) [14] compared the effect of levodopa on tremor, rigidity, and bradykinesia [15]. To this end, changes of the UPDRS motor subscores for these three motor signs from the first, placebo-controlled part of the study were compared. During the first 40 placebo-controlled weeks of the study levodopa led to an improvement in the UPDRS motor score as compared to placebo [14]. The motor effect of levodopa increased from week 4 to week 22 of treatment and stabilized thereafter, suggesting that levodopa's effect on motor symptoms builds up over weeks. The magnitude of effect on bradykinesia, rigidity and tremor was comparable at 4, 22, and 40 weeks of treatment, confirming a similar effect of levodopa on all cardinal motor features in early PD. However, patients with disabling motor symptoms including severe resting tremor were not included in the study [14, 15].

MAO-B und COMT inhibitors

The effect of selegiline add-on to levodopa was studied in a small double-blind placebo controlled cross-over study with treatment periods of 8 weeks separated by a 4-week washout. Despite a reduction of levodopa dose in the selegiline arm, an improvement of tremor was observed in the 10 mg selegiline arm [16]. Lew performed a post-hoc analysis of 4 pivotal trials of rasagiline focusing on its effects on tremor [17]. The UPDRS cumulative subscore for resting and action tremor (item 16 UPDRS part 2 plus items 20 and 21 UPDRS part 3) served as outcome. In both rasagiline monotherapy studies (TEMPO, ADAGIO) the change of the cumulative tremor score at the end of the active treatment period was significantly different from placebo. However, the absolute change was minimal (approx. 0.5 points worsening on placebo vs. no change on rasagiline after 6 or 9 months, respectively). In the rasagiline add-on studies in patients with motor fluctuations (PRESTO, LARGO), rasagiline significantly improved tremor compared with placebo. An almost identical improvement of tremor was evident with entacapon in the LARGO trial. In both trials the absolute reduction of tremor scores by rasagiline was minor. However, a somewhat more marked effect was evident in a subgroup with severe baseline tremor in the LARGO trial [17]. In line with these findings, a post-hoc analysis of two safinamide add-on therapy trials (Studies 016 and SETTLE) found safinamide to improve tremor compared with placebo [18].

Oral dopamine agonists

Early studies on the effect of dopamine agonists in PD tremor were reviewed by Elble [19]. Overall, their antitremor effect appeared comparable with levodopa in those initial studies [19]. Pogarell et al. treated 84 early to moderately advanced PD patients with marked or “drug resistant” tremor [20]. However, at study baseline only 70 patients were on levodopa with a median daily dose of 300 mg. Patients were randomized to pramipexole (n=44) or placebo (n=40) as add-on to levodopa. Up titration lasted up to 7 weeks and was followed by a 4-week maintenance period. The absolute change in the tremor subscore of the UPDRS (item 16 UPDRS part 2 plus items 20 and 21 UPDRS part 3) served as primary outcome. All pramipexole and all but two placebo patients completed the trial. The median pramipexole hydrochloride dose during maintenance was 4.1 mg. Pramipexole was significantly superior to placebo with a reduction of the UPDRS tremor subscore of -5.5 (-48% compared to baseline) vs. -1.5 (-14%) with placebo, corresponding to a difference in the mean percentage change of -34.7% in favor of pramipexole. The difference was significant for resting and

action tremor. The treatment effects increased during dose titration and remained stable during the maintenance period. The side effect profile was compatible with rates of adverse events of non-ergot dopamine agonists in other trials [20]. The main limitation of this study is the low median levodopa dose suggesting that most patients were not really levodopa resistant.

Navan et al. performed a double-blind, randomized, parallel group trial in 30 PD patients with upper limb tremor who had never taken a dopamine agonist [21]. Patients were randomized to pramipexole (n=10), the ergot agonist pergolide (n=10), or placebo (n=10). Treatment lasted for 3 months and included a titration period of up to 10 weeks. Maximum doses in the pramipexole hydrochloride and pergolide arm were 4.5 mg, each. The UPDRS motor score and a custom-made tremor scale (tremor index, maximum score 30 points) assessing resting and postural tremor in the more affected upper limb as well as spiral drawing with the same hand served as primary outcomes. The majority of patients were on stable medication with about half of the patients taking levodopa at mean daily doses in the different treatment arms between 383 mg and 550 mg. There were two dropouts in the placebo group. Four patients in the pergolide arm but no patient in the pramipexole arm dropped out because of adverse events. One patient in the pergolide group and one patient in the pramipexole group did not reach the target dose because of side effects. At the end of the study 8/9 subjects on placebo considered themselves as receiving placebo and 18/20 patients on dopamine agonists recognized that they were on active treatment. Pramipexole and pergolide were superior to placebo in alleviating tremor, demonstrated by a significantly stronger reduction in the tremor index and UPDRS motor score than placebo. The difference between the two dopamine agonists was not significant [21]. The study suggests that the improvement of tremor is probably a class effect of dopamine agonists. However, the low patient number, the high drop-out rate, especially in the pergolide arm, the unusual, unvalidated end point and potential unblinding represent substantial limitations of the study.

Schrag et al. investigated the antitremor effect of ropinirole by post hoc analysis of three randomized, double-blind multicenter studies involving a total of 844 early PD patients without dopaminergic treatment at baseline [22]. The effect of ropinirole, bromocriptine, levodopa and placebo on rest and action tremor (UPDRS motor score items 20 and 21, respectively) were compared. Ropinirole, bromocriptine and levodopa, but not placebo, led to a significant improvement of resting tremor without difference between the active treatment arms. Possibly due to low baseline action tremor scores, ropinirole did not lead to a significant improvement of action tremor in the placebo-controlled study. The effect of other active

treatments on action tremor was not significantly different from ropinirole in the two other studies. The effect of ropinirole and levodopa on tremor was identical in the levodopa-controlled study [22].

The antitremor effect of add-on pramipexole was confirmed in a post hoc analysis of a randomized, placebo-controlled trial in 354 advanced PD patients. At the end of the 26 weeks treatment period, the improvement of cumulative UPDRS tremor score (items 16, 20, and 21) was significantly in favor of pramipexole. The difference in change of tremor scores was significant in subgroups of patients with high and low baseline tremor scores [23].

The antiparkinsonian effect of the non-ergot agonist piribedil in early PD was studied in a randomized, placebo-controlled study. Four hundred and five patients were included. UPDRS motor subscores served as secondary outcomes. Following 7 months of treatment, an average dose of 240 mg piribedil led to significant reduction in resting (item 20) and action tremor (item 21) [24]. Furthermore, the antitremor effect of transdermal rotigotine was demonstrated in a post hoc analysis of 3 randomized, placebo-controlled trials (one monotherapy and two add-on trials of 12 weeks each; [25]).

Apomorphine

Apomorphine is a short-acting non-ergot dopamine D1, D2, and D3 receptor agonist. The drug is used as subcutaneous bolus injection for early morning akinesia and other off periods or as subcutaneous (sc.) infusion ("pump" treatment) for patients with severe motor complications. A sublingual formulation was approved recently. Apomorphine is the only antiparkinsonian agent with an efficacy on motor symptoms comparable to levodopa. No data from placebo-controlled trials on the specific antitremor effect of apomorphine are available.

Hellmann et al. examined the acute effect of increasing doses of apomorphine (1, 2, and 4 mg administered sc.) on bradykinesia, rigidity, and tremor in an uncontrolled, open-label study [26]. Eighteen patients responsive to levodopa and without motor fluctuations were included. Apomorphine injections were performed >12 h after the last intake of antiparkinsonian medication. The change in UPDRS motor score and subscores for limb bradykinesia (items 23-26), rigidity (item 22), and resting and action tremor (items 20 und 21) from baseline served as outcome parameters. Fifteen patients tolerated the maximum dose, one subject 2 mg and two subjects only 1 mg. The highest tolerated apomorphine dose led to an improvement of the UPDRS motor score from 31.5 to 20 points. Tremor, rigidity, and bradykinesia improved without significant differences between individual motor symptoms [26].

Two single dose, open-label studies described above found an equivalent beneficial effect of apomorphine (mean dose 2.4 and 2 mg, respectively) and 250 mg levodopa on tremor [8, 9]. Schrag et al. compared the acute effect of an individually effective dose of sc. apomorphine with the anticholinergic biperiden (5 mg iv.) on bradykinesia, rigidity, and tremor [27]. For inclusion, patients had to have tremor and to be overall responsive to apomorphine. Ten of the 17 patients had motor fluctuations and all of the patients receiving chronic levodopa had an excellent response. Apomorphine and biperiden were administered in random order on two consecutive days during practically defined off. Amplitude and frequency of resting, postural and kinetic tremor in the more affected hand were assessed using accelerometry, with the examiner blind to the administered agent. Change in UPDRS motor subscores for bradykinesia (items 16, 23-26) and rigidity (item 22) vs. baseline served as additional endpoints. All subjects receiving apomorphine and 16/17 patients receiving biperiden showed a reduction in resting, postural, and kinetic tremor amplitude. None of the drugs altered tremor frequency. Resting tremor amplitude reductions by apomorphine and biperiden were 98 and 67% on average. Postural tremor was reduced by 60% with apomorphine and 65% with biperiden. Reduction of kinetic tremor was 62% with apomorphine and 79% with biperiden. This difference in favor of biperiden may have resulted from higher baseline action tremor scores on the biperiden than on the apomorphine day. Only apomorphine, but not biperiden, led to a significant improvement of rigidity and bradykinesia (by 58 and 48%, respectively) [27]. A limitation of this study is that all patients had to be apomorphine-responsive and all patients on chronic treatment had to show a good overall response of motor symptoms to levodopa. A good response to apomorphine could therefore be expected.

Anticholinergics

Anticholinergics are held to be especially efficacious in the treatment of PD tremor. In a comparative trial of 2 weeks treatments with levodopa, trihexiphenidyl, and amantadine described above [5], levodopa and the anticholinergic had a comparable beneficial effect on tremor amplitude, although some patients showed a markedly better response to levodopa and others to trihexiphenidyl. In the comparative single dose trial of sc. apomorphine and iv. biperiden, described above [27], apomorphine and the anticholinergic had a comparable beneficial effect on tremor, but only apomorphine led to a significant improvement of rigidity and bradykinesia. In line with this finding, in a recently published single dose study comparing levodopa with biperiden [11], the acute effect of anticholinergic treatment was

largely limited to tremor whereas dopaminergic treatment improved tremor, bradykinesia, and rigidity to a similar degree.

A review sponsored by the Cochrane Collaboration found the antitremor effect of anticholinergics not convincingly different from its effect on other cardinal motor features [28]. Nine studies involving 221 subjects fulfilled criteria for inclusion [29-37]. All had a double-blind cross-over design with study durations between 5 and 20 weeks (2 to 10 weeks on actual treatment). Drugs investigated were trihexiphenidyl (*aka* benzhexol), orphenadrine, benztropine, bornaprine, benapryzine, and methixine. Seven studies investigated anticholinergics as add-on to other antiparkinsonian treatment regimes, which were kept stable during the trials. Incomplete reporting of methodology including lack of information on doses used in the trials, varied outcome measures including use of custom-made scales in many of the studies and incomplete reporting of results precluded combined statistical analysis. Five studies used tremor and other motor symptoms as outcome parameters. These studies revealed variable results from an improvement only of tremor in some to an improvement of other motor symptoms but not of tremor in other studies. With the exception of one study using methixine, all studies found an improvement in at least one outcome with anticholinergic treatment. The only study using a validated outcome (the Webster scale) for all parkinsonian features [30] found a 52% improvement of tremor by bornaprine vs. a 19% improvement on placebo. By contrast, bradykinesia, rigidity, and axial symptoms were only mildly improved by bornaprine.

Amantadine

Amantadine is mainly used for the treatment of motor complications, in particular dyskinesias. Randomized studies with a new extended release (ER) formulation of amantadine also demonstrated a significant off time reduction with amantadine [38]. Most studies on the symptomatic effect of amantadine in PD without motor complications were conducted in the early 1970s and do not meet current methodological standards. Only few of the older studies provide details on the size of its antitremor effect.

Parkes et al. compared the effect of the anticholinergic trihexiphenidyl (8 mg per day), amantadine (daily dose 200 mg), and a combination of both drugs over 4 weeks each, in a randomized, double-blind cross-over design [39]. These treatments were followed by 6 months of individualized open-label titration of levodopa (without decarboxylase inhibitor) up to 750-3000 mg. Seventeen patients were included; 15 of them had PD and all but one had tremor. A custom-made, unvalidated motor scale served as primary outcome. Improvement of

tremor amounted to 17% with amantadine, 4% with trihexiphenidyl, 35% with the combination of both, and 52% with open-label levodopa [39].

One study compared amantadine (daily dose 200 mg) and placebo in 30 parkinsonian patients, 27 of whom discontinued previous medication [40]. Three patients continued their co-treatment with anticholinergics or antihistamines. Amantadine and placebo were administered in a double-blind cross-over design for two weeks each in random order. The 26 patients completing the study showed a mean 17% improvement of tremor (vs. a mean 8% improvement with placebo) [40]. The short-term cross-over study comparing the effect of levodopa and amantadine on tremor in untreated tremor-dominant PD [5] described above showed only a 23% improvement of tremor amplitude with amantadine. By contrast, tremor was improved by 59% with trihexiphenidyl and by 55% with levodopa. Of the 9 patients, 5 preferred to continue with trihexiphenidyl, 4 with levodopa and none with amantadine [5].

A recent post-hoc analysis of pooled data from two phase III trials of ER amantadine found a significant improvement of on time activities of daily living (using part 2 of the MDS UPDRS) with ER amantadine as compared to placebo [41]. The difference in ADLs was mainly driven by improvements in mobility and tremor with MDS UPDRS item 2.10 improved by 31% with ER amantadine vs. 10% with placebo [41].

Beta blockers, primidone, and clonazepam

Several small studies point towards a possible effect of propranolol and other beta-adrenoceptor antagonists (beta blockers) on PD resting and action tremor [10, 42-44].

Koller et al. compared the effect of long-acting propranolol, primidone, and clonazepam on PD resting and action tremor in a double-blind cross-over study [44]. Ten non-fluctuating patients were included with prominent tremor despite treatment with levodopa (average dose 500 mg), in 4 cases also with trihexyphenidyl. Tremor was evaluated by accelerometry after dose titration and one month of stable treatment with 160 mg propranolol, 250 mg primidone, or 4 mg clonazepam. The order of treatment was randomized but it is unclear if a drug washout was performed between individual treatments. Eight of ten patients noted a marked improvement of tremor on propranolol. Only one patient each preferred primidone or clonazepam. The average reduction of tremor amplitude on propranolol was 70% for resting and 50% for postural tremor. Neither primidone nor clonazepam had a relevant influence on resting or postural tremor amplitude and none of the drugs altered kinetic tremor [44].

Another study described above [10] used accelerometry to compare the effect of single doses of levodopa, propranolol, and placebo on resting and postural tremor in 11 levodopa-

responsive PD patients in a blinded fashion. On the highest dose of propranolol (80 mg), four PD patients showed a >30% reduction of resting tremor amplitude and 3 patients a >30% amplitude reduction of postural tremor, but overall tremor response to propranolol was not significantly different from placebo [10].

A Cochrane Review on treatment of PD with beta blockers including the study by Henderson et al. found no conclusive evidence for an effect of beta-blockers in PD [45]. Four studies (two with oxprenolol and another two using propranolol) including a total of 72 patients fulfilled inclusion criteria for review [10, 42, 46, 47]. Despite being randomized, double-blind, cross-over all four studies had methodological flaws preventing conclusions on the actual beta blocker effect on PD tremor.

Clozapine

Clozapine is the drug of choice for the treatment of severe PD psychosis. First open studies suggesting an effect of clozapine on PD tremor were published in the 1980s and early 1990s [48-51]. Three of these open-label studies included only patients with drug-resistant tremor, including patients with tremor refractory to anticholinergics [49-51].

In 1997 two randomized, controlled studies on the effect of clozapine on PD tremor were published. Friedman et al. compared the effect of clozapine and benztropine in a randomized, double-blind, cross-over design [52]. Two 6-weeks treatment periods with clozapine or benztropine were separated by a 2-week washout period, followed by another treatment period with the other agent. Following unblinding, patients could opt for open-label treatment with clozapine or benztropine. Initial doses and weekly dose increases were 12.5 mg for clozapine and 0.75 mg for benztropine with possible maximum doses of 75 mg for clozapine and 4.5 mg benztropine. The total daily dose was divided into two single doses. The UPDRS activities of daily living tremor question (item 16) and the Fahn-Tolosa-Marin-Tremor Score served as primary outcomes. Adverse events were systematically recorded. Of the 22 included subjects, 2 dropped out for side effects, another dropped out for other medical reasons. Tremor ratings at baseline were not significantly different from ratings at the end of the washout period. Tremor scores were improved by about one third by clozapine (mean dose 39 mg) and benztropine (mean dose 3.0 mg). Blinded video rating revealed the best tremor control in 9/19 patients with clozapine and in another 9 patients with benztropine. Benztropine was associated with a higher rate of at least moderate adverse events than clozapine, with dry mouth and impaired cognition being the side effects most commonly reported. Following unblinding, 4/19 patients opted for open-label clozapine and 5 for open-

label benztropine. The authors concluded that the average antitremor effect of both drugs is comparable [52].

Bonuccelli et al. examined the acute effect of 12.5 mg clozapine or placebo on resting and action tremor in 17 PD patients (5 with and 12 without motor fluctuations) in the practically defined off state [53]. The reduction in the UPDRS score for resting and action tremor in the right upper extremity served as primary outcome, although it is unclear if this outcome was predefined in the protocol. The order of treatments was randomized, and the study was double-blind. Fifteen of 17 patients were responders, showing more than 50% improvement of tremor. Tremor reduction was significantly greater on clozapine than on placebo. The duration of sedation was somewhat shorter than the effect of clozapine on tremor. The 15 responders went on to receive open label clozapine at a mean dose of 45 mg over 15.5 months on average. All patients treated openly reported an improvement of tremor. According to the authors, sedating side effects of clozapine waned over time and no patients developed tolerance to the antitremor effect of clozapine [53].

A large retrospective study of the effect of clozapine on non-motor and motor symptoms including tremor was published in 1998 [54]. One hundred and six of the 172 patients included suffered from resting tremor. In 26 of the patients included, tremor was the reason for starting clozapine. At a mean clozapine dose of 31 mg, tremor abated in 16% of the patients. Forty two percent of the patients showed a marked improvement of tremor, 41% no change. In addition, a randomized study of the efficacy of clozapine in PD psychosis demonstrated an improvement of tremor as compared to placebo [55]. None of the studies found a worsening of other motor symptoms on clozapine.

The use of clozapine is generally limited by the adverse events profile of the drug [56], most importantly by a 1% risk of agranulocytosis. This risk is especially high during the first 18 weeks of treatment and makes regular blood tests necessary. Other side effects of clozapine include sedation, drooling, orthostatic hypotension, dizziness, and QT-time prolongation. In addition, metabolic side effects (weight gain, hypercholesterolemia, and insulin resistance) and an increased risk of thromboembolism have to be considered.

Zonisamide

Zonisamide, chemically a sulfonamide, was developed in Japan as an anticonvulsant drug. Only later, it was shown that the drug is a mixed MAO-B inhibitor, sodium and T-type calcium channel blocker, and glutamate release inhibitor [2]. In 2001, Murata reported on the improvement of parkinsonism in a PD patient who was treated with zonisamide for

coincidental seizures [57]. In a randomized double-blind 3-month study the effect of 25 and 50 mg zonisamide on motor fluctuations was compared with placebo [58]. Off time reduction was significantly higher in the 50 mg zonisamide group (about 0.7 h) than with placebo (no change). Based on these results, zonisamide was classified as efficacious and clinically useful in the treatment of motor fluctuations by the recent MDS evidence-based review on the treatment of PD [2]. Small open-label studies reported on an improvement of tremor by up to 200 mg zonisamide [59-61]. A narrative review found that in most patients the drug has only a relatively mild effect on tremor but some patients may show significant improvement, which may be marked on high doses up 400–500 mg [62]. An illustrative video case with excellent tremor response was published by a Japanese group [63].

Adenosine A2A receptor antagonists

In several randomized controlled trials, the adenosine A2A receptor antagonist istradefylline led to an improvement in motor complications with a reduction of daily off time in PD [64]. However, due to equivocal study results, the drug was classified as only likely efficacious and possibly useful in the treatment of motor fluctuations in the recent MDS evidence-based review [2]. In a pilot study involving 15 patients, 80 mg istradefylline added to a subtherapeutic dose of levodopa led to a marked improvement of rest tremor [65]. Subsequent studies did not show a consistent improvement of motor symptoms by istradefylline during on periods [2].

Cannabinoids

A systematic review and meta-analysis of the motor and non-motor effects of cannabinoids in PD was published recently [66]. The authors found no compelling evidence to recommend the use of cannabinoids in PD but identified potential benefits in the treatment of tremor and a number of non-motor symptoms. An open-label, single dose study reported an improvement of PD tremor after smoking medical cannabis [67]. Several open-label studies using telephone interviews or mail or telephone surveys reported on a beneficial effect of inhaled cannabis or oral cannabinoids (tetrahydrocannabinol, cannabidiol, or mixed preparations) on tremor (reviewed in [66]). One of five randomized controlled studies of cannabinoid treatment in PD focused on tremor [68]. In this crossover trial 24 PD patients underwent two single-dose experiments to evaluate the acute effect 300 mg oral cannabidiol (CBD) or placebo on anxiety and tremor induced by a simulated public speaking test. CBD attenuated anxiety and tremor amplitude (measured using accelerometry) elicited by

simulated public speaking. The results suggest that CBD may be a beneficial in PD patients with anxiety-related tremor but does not confirm a direct effect of CBD on tremor [68]. Another randomized controlled trial found a beneficial effect of the synthetic cannabinoid nabilone on PD non-motor symptoms, in particular anxiety and sleep problems [69]. According to a recently published patient survey, substantially more PD patients observed an improvement of tremor with tetrahydrocannabinol (THC) or mixed preparations than with CBD [70]. Cannabinoids may be a class of drugs with the potential to ameliorate PD via the improvement of stress and anxiety, common problems in PD. Since CBD lacks psychotropic effects, it is of particular interest in the PD population and warrants further study. In real life, many CBD products contain various levels of THC and other contaminants and even highly purified CBD preparations are associated with adverse events when dosed adequately [71].

Botulinum toxins

The effect of BoNT-A on parkinsonian upper limb tremor was investigated in 4 open-label studies [72-75] and one randomized, placebo-controlled study [76]. A small case series described the successful treatment of jaw tremor in PD with BoNT-A [77].

Trosch and Pullman treated 12 PD patients with disabling upper limb tremor in an open-label design with single injections of onabotulinumtoxin A (Botox®) [73]. The authors performed electromyography (EMG)-guided injections of onabotulinumtoxin A (mean dose 107 U) into arm and forearm muscles involved in tremor generation in the most affected upper limb. Six of 12 patients showed no initial effect and received booster injections after 3 weeks. Follow up 6 weeks after the initial injection showed no significant changes of tremor on accelerometry in the PD group with tremor amplitude reduced by >50% in only 2 patients. Side effects were generally mild but one patient had marked weakness of finger extensors [73]. In an open-label prospective analysis of outcomes after onabotulinumtoxin A (Botox®) treatment in patients with limb disorders, Pullman reported on single-injections of disabling tremor in 15 PD patients. Average efficacy of BoNT-A for PD upper limb tremor was 36% [74].

Rahimi et al. treated 28 PD patients in an open-label prospective design 3 times with intervals of 16 weeks with incobotulinumtoxin A (Xeomin®) [75]. They injected shoulder, arm, and forearm muscles of the more affected upper limb. Muscle selection was based on an individual kinematic tremor analysis. Injected muscles and dose could be adapted for each treatment session. Fahn–Tolosa–Marin (FTM) Tremor Rating Scale scores and UPDRS scores for resting and action tremor in the affected and contralateral upper limb at the time of

injection and after 6 weeks served as outcome parameters. Fifteen completed the study. Treatment led to a significant reduction of the UPDRS resting tremor score in the injected limb from mean 2.7 at baseline to 2.0 at week 16 and to 2.1 at week 32. Reduction of action tremor was not significant. Global tremor severity, as measured with the FTM score, was significantly reduced. A trend for functional improvement was found in 7/28 patients in whom upper limb tremor was the most disabling symptom [75]. The results of this study suggest that BoNT-A injections may lead to functional improvement in PD patients with upper limb tremor. Similar to other studies, muscle weakness represented a significant limitation of BoNT-A treatment. Samotus et al. presented 2-years follow up data of the study [78]. Fifteen of the 28 patients originally reported [75] received the sixth BoNT-A injection at 80 weeks (treatment interval 16 weeks) [78]. According to the authors the improvement was maintained but the injections did not lead to an improvement of quality of life measured with a visual analogue scale.

In 2017, Mittal et al. published the first double-blind, randomized, placebo-controlled study on the treatment of upper limb tremor in PD with BoNT-A [76]. In a cross-over design, 34 were first treated with incobotulinumtoxin A (Xeomin®) or saline. The cross-over took place 12 weeks after the first injection. Patients received 7-12 (mean 9) EMG-guided injections into forearm and hand muscles including the lumbricals. Although not explicitly noted in the manuscript, only the more affected upper limb was injected (personal communication with the first author). Muscle selection was based on clinical observation. Clinical assessments were performed at baseline and 4 and 8 weeks after the injections. The change in UPDRS scores for resting tremor at 4 and 8 weeks following BoNT-A or placebo served as primary outcome. Secondary outcomes included subjective tremor severity (UPDRS item 16), UPDRS score for action tremor, the NIH Collaborative Genetic Criteria (NIH CGC) tremor severity score, Patient Global Impression of Change (PGIC) and the Parkinson's Disease Quality of Life Questionnaire. Thirty of 34 of the randomized patients completed the study. No patient dropped out for side effects. Injected doses of incobotulinumtoxin A varied between 85 and 110 U (mean 100 U). Change in UPDRS resting tremor after BoNT-A was significant at 4 and 8 weeks compared with placebo (median improvement by 1 point vs. 0 points with placebo). The reduction of action tremor was significant 8 weeks following BoNT-A. UPDRS activities of living tremor score, NIH CGC tremor score and patient global impression were improved at 4- and 8-weeks post injection compared with placebo. Improvement in quality of life was not significant. Ten of 27 patients in the BoNT-A group showed decreased strength in ergometric assessment, which was not perceived by 5,

perceived as subtle and moderate to severe in 2 patients. Hand weakness was reported in a lower proportion of subjects following saline injection [76]. The low number of subjects, the one-time active treatment and short duration of the treatment periods (12 weeks), possibly leading to a carry-over effect in the subjects first treated with BoNT-A, represent limitations of the study.

Schneider et al. reported on the one-time open-label injection of 3 PD patients with disabling jaw tremor with abobotulinumtoxin A (Dysport®) [77]. A bilateral injection of a mean dose of 53 U into each masseter muscle led to an improvement of jaw tremor in all three treated subjects, documented by video recordings some weeks after injection, without side effects. A single observation in patients with hereditary chin tremor [79] supports the use of BoNT-A injects for the treatment of chin tremor in PD.

Other and investigational drugs

The antitremor effect of the α2δ calcium channel subunit modulator gabapentin was tested in a placebo-controlled, double-blind, crossover trial in 19 patients with advanced PD. Gabapentin led to an improvement in total UPDRS and UPDRS tremor scores. However, tremor quantification using surface EMG revealed no significant improvement [80]. A subsequent placebo-controlled, crossover trial of gabapentin in patients with motor complications found no change in PD tremor [81].

The antidepressant mirtazapine, a central presynaptic alpha2 receptor antagonist enhancing serotonin and norepinephrine neurotransmission was tested as an antitremor drug in an open label study in 25 PD patients [82]. UPDRS tremor scores (items 16, 20, and 21) served as primary outcome. Mirtazapine led to a very modest improvement of tremor scores (overall 7%). The drug was not further studied in this indication.

Zuranolone (SAGE-217) is a novel GABA-A receptor positive allosteric modulator (PAM). The antitremor effect of zuranolone in PD was recently tested in a small prospective open label study in 14 patients. Following one week treatment, MDS UPDRS part 2 and 3 tremor scores improved by 40%. The most common adverse events were dizziness, sedation, and somnolence. The authors conclude that the study results support the further investigation of GABA-A receptor PAMs as adjunctive treatments for PD tremor [83].

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