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July 24, 2009

DRUG INFORMATION

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Dear Mr. Faller:

Thank you for discussing AGGRENOX® capsules (aspirin/extended-release dipyridamole 25mg/200mg) and MIRAPEX® Tablets (pramipexole) with your Boehringer Ingelheim Pharmaceuticals, Regional Manager, State Government Affairs, Penny Atwood. For requested information for formulary review including recent topic(s) such as the following:

- AMCP Dossiers for AGGRENOX and MIRAPEX (separate attachments)
- The PRoFESS Trial (see pages below within this attachment)
- Headache Incidence and Management with AGGRENOX
- Dose Titration for AGGRENOX
- DOMINION Results (MIRAPEX)
- Calm-PD Study (Mirapex vs Levodopa)
- Antidepressant Effects of MIRAPEX

If you did not request this information, please contact our Drug Information Unit Call Center at 1-800-542-6257 (option #4).

AGGRENOX is indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis. Any other use not included in the package insert(s) is an investigational use and cannot be recommended by Boehringer Ingelheim Pharmaceuticals, Inc.

MIRAPEX Tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease and moderate-to-severe primary Restless Legs Syndrome (RLS). Any other use not included in the package insert(s) is an investigational use and cannot be recommended by Boehringer Ingelheim Pharmaceuticals, Inc.

Thank you for your interest in AGGRENOX capsules and MIRAPEX Tablets. If you should have any further questions, please do not hesitate to contact the Drug Information Unit.

Sincerely,

The Drug Information Unit Healthcare Professional Staff
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BLAPIERRE/2009-019917
AMCP Dossiers

The AMCP dossiers (separate attachments) are intended to provide clinical and outcomes data that are useful for formulary review. The Drug Information Unit is available to answer questions regarding the content of this material. Please contact your Boehringer Ingelheim Pharmaceuticals, Regional Manager, State Government Affairs, Penny Atwood for the scheduling of consultations.

The PRoFESS Trial

The PRoFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial was a multicenter, randomized, double-dummy, double-blind active and placebo controlled trial designed to compare the fixed combination of low-dose (25 mg) aspirin (ASA) and (ER DP) extended release dipyridamole (200 mg) given twice daily with clopidogrel (75 mg) tablets given once daily for recurrent stroke prevention. Also, in a second simultaneous randomization, (80mg) of Micardis® (telmisartan) was given once daily, and compared to placebo on the same endpoint. The trial utilized a 2 x 2 factorial design in a large, diverse patient population (n = 20,332), involving 695 centers from 35 countries.[1] PRoFESS was initially designed to compare the efficacy and safety of ASA + ER DP with the combination of clopidogrel plus aspirin; however the study design was amended early after the MATCH trial showed that adding ASA to clopidogrel in patients presenting with transient ischemic attack or minor stroke provided little additional benefit, but significantly increased the bleeding risk.[1, 2, 3] The 2027 patients initially allocated to the clopidogrel + ASA group had been treated for up to 8 months, before they were switched to clopidogrel alone at the time of the amendment. The remaining 18,305 patients were subsequently randomized to ASA + ER DP or clopidogrel alone.[3]

The primary outcome of the PRoFESS trial was the time to first recurrent stroke over the course of the study, using a time-to-event analysis. The most important secondary outcome was the composite of stroke, myocardial infarction or vascular death. Additional secondary outcomes include the aforementioned composite plus congestive heart failure, new-onset diabetes, other designated occlusive vascular events (pulmonary embolism, deep-vein thrombosis, peripheral arterial occlusion, transient ischemic attack, cerebral venous thrombosis or retinal vascular accident not classified as stroke), any death, stroke subtype by Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria and Mini Mental State Examination score. The risk of major hemorrhagic events was assessed during the safety evaluation.[1]

Inclusion and Exclusion criteria:

Patients included in PRoFESS were individuals who were ≥ 55 years old, and who had had an ischemic stroke within 90 days of entry to the study. The study also included patients aged 50–54 years and/or 91–120 days after the qualifying stroke provided the patient had two of the following additional risk factors: diabetes mellitus, hypertension, smoker at time of qualifying stroke, obesity (BMI > 30), previous vascular disease (stroke, MI, or peripheral arterial disease), end-organ damage (retinopathy, left ventricular hypertrophy, or microalbuminuria), or hyperlipidemia. Further, eligible patients had to be clinically and neurologically stable prior to being randomized, and not deteriorating or having a progressive stroke or other condition. The diagnosis of the ischemic stroke was based on the investigator's clinical judgment, and supplemented with evidence on a CT scan or other imaging modality, such as MRI of the brain. Positive evidence on brain imaging was not required to diagnose stroke if symptoms lasted greater than 24 hours, but brain imaging which confirmed the presence of a new brain infarct consistent with the clinical syndrome was required if symptoms lasted less than 24 hours. Eligible patients who had stents were also allowed to enroll in PRoFESS, however, patients who have undergone a carotid endarterectomy were excluded. Some other exclusion criteria preventing patients from being enrolled in the study were: presenting with a primary hemorrhagic stroke, known brain tumor, pre-stroke history of dementia requiring institutional care, a modified Rankin scale score > 4 at baseline, a patient who was unlikely to be released from the hospital following the qualifying stroke, uncontrolled hypertension, and known severe renal insufficiency or severe hepatic dysfunction. For a more complete listing of all PRoFESS trial inclusion and exclusion criteria, please refer to reference number one.[1]

Baseline Characteristics:

Table 1 shows the baseline characteristics for the study population entering the PRoFESS trial. The average age of patients entering the study was 66.1 ± 8.6 years, and 36% were females. Almost 25% of the PRoFESS patients had a

history of stroke or TIA prior to the index stroke; 47% had hyperlipidemia, 74% were hypertensive, 28% were diabetic, and 16% had ischemic coronary artery disease. Within 10 days from the qualifying event, 39.9% of patients were randomized into the study, and 15 days was the median time to randomization. The qualifying events of patients enrolled in PRoFESS according to the TOAST criteria were: 28.5% of strokes due to large artery atherosclerosis, 52.1% to small-vessel disease (lacune), 1.8% to cardioembolism, 2.0% to other determined etiologies, and 15.5% were strokes of undetermined etiology. The four most commonly used concomitant medications at randomization were statins (47.2%), ACE inhibitors (36.8%), calcium channel blockers (24.2%) and beta-blockers (20.7%). The mean blood pressure at randomization was 144/84 mmHg, and the mean BMI was 26.8. The median score of the first Mini Mental State Examination administered during the study was 28, measured 30 days post baseline.[1, 3]

Table 1: Baseline Patient Demographics for PRoFESS[1]

Total patients	**20,332**
Mean age, years	66.1
Gender, % female	36.0
Race or ethnic group (%)	
South Asian	8.4
Chinese	18.0
Japanese	1.1
Malay	0.6
Other Asian	4.6
Arab, Persian	0.2
Black African, African Americans	4.0
European, Caucasian	57.3
Native Latin	4.5
Caribbean Hispanic	0.3
Other	0.8
Median time from qualifying event to randomization, days	15
Time groups, %	
≤10 days	39.9
11-30 days	29.0
≥ 31 days	31.1
Medications at baseline (%)	
ACE inhibitors	36.8
ARBs	5.2
Beta-blockers	20.7
Loop active diuretics	3.2
Thiazide diuretics	17.1
Potassium-sparing diuretics	1.5
Calcium channel blockers	24.2
Statins	47.2
Fibrates	1.
Insulin	5.6
Oral hypoglycemics	18.6
Risk factors, %	
Current smoker	21.2
Former smoker	36.2
Regular alcohol consumption (>1 drink per week)	35.4

Physical examination (mean)	
BP mmHg	144/84
BMI	26.8
Waist circumference, cm	96.5
Modified Rankin scale, %	
Score 0	14.1
Score 1	37.3
Score 2	25.0
Score 3-5	23.7
TOAST classification, %	
Large-artery atherosclerosis	28.5
Cardioembolism	1.8
Small-artery occlusion (lacune)	52.1
Acute stroke of other etiology	2.0
Stroke of undetermined etiology	15.5
Median MMSE (Mini Mental State Examination)	28
MMSE groups, %	
Score < 25	17.4
25-27	21.1
28	13.3
29	19.1
30	29.1
Medical history, %	
Previous stroke (prior to qualifying stroke)	18.3
TIA	8.6
MI	6.7
CHF	2.6
PAOD	2.9
Hypertension	73.8
Diabetes mellitus	28.1
Hyperlipidemia	46.6
Ischemic coronary artery disease	16.2
Atrial fibrillation	2.6
Valvular disease	1.7
Deep venous thrombosis	1.5
TIA = Transient ischemic attack	

CHF = congestive heart failure
PAOD = peripheral arterial obstructive disease
CCB = calcium channel blocker; BP = blood pressure BMI = body mass index
MMSE = Mini Mental State Examination

Study Design and Treatment Schedule:

Patients who had consented to participate in PRoFESS, and who met the entry criteria were randomized in a double-blind fashion to receive either ASA + ER DP (25 mg/200 mg twice daily) or clopidogrel (75 mg once daily) as well as either telmisartan (80 mg once daily) or placebo as shown in the figure below.[1]

PRoFESS Trial Design.[1]

	ASA + ER DP	**Clopidogrel**
Telmisartan	ASA + ER DP + Telmisartan (n=5000)	Clopidogrel + Telmisartan (n=5000)
Placebo	ASA + ER DP + Placebo (n=5000)	Clopidogrel + Placebo (n=5000)

All patients were treated for hypertension, if necessary, using standard open-label blood pressure medications permitted by the study protocol. Patients were informed as to which analgesic medications were permitted, and investigating physicians were encouraged to control blood pressure based on current guidelines for blood pressure control, and to manage other risk factors. A diuretic would be the first recommended blood pressure-lowering drug to be added if necessary, followed by a beta-blocker, or a calcium channel blocker. Angiotensin receptor antagonists were not allowed in PRoFESS, but the addition of ACE inhibitors was permitted. Other restricted medications included anticoagulants (excluding short-term use of anticoagulants), ASA-containing medication, other platelet inhibitors, thrombolytic agents and glycoprotein IIb/IIIa inhibitors. Also, special instructions were provided to investigators for managing patients with headache, to reduce the amount of patients discontinuing the study medication due to this adverse event.[1]

Patients could be randomized while still in the hospital following the qualifying stroke, depending upon qualifications and risk factors, or up to 120 days following the stroke. Patients were evaluated at hospital discharge, or after one week, whichever came first, and again at 1 month, 3 months and 6 months. For the remainder of the study, clinic visits were scheduled every 6 months, with a telephone contact scheduled approximately halfway between each visit.[1]

An independent Data Monitoring Committee regularly monitored the results of the trial. When approximately one third and two thirds of stroke outcome events occurred, two interim efficacy analyses were performed. An independent adjudication and assessment committee verified all primary and key secondary outcomes blinded to treatment allocation. At least 2 adjudicators reviewed all strokes, as well as most other adjudicated events according to established protocols and procedures. If a randomized patient suffered a stroke, the TOAST criteria were used to classify the stroke as soon as possible after the event. To assess the degree of disability, the modified Rankin scale assessment was repeated three months after the secondary stroke, and the Barthel activities of daily living index was administered.[1]

PRoFESS Efficacy Results:

The primary outcome was time to first recurrent stroke with a pre-specified non-inferiority margin. Across an average observation time of 2.5 years, the primary outcome of first recurrent stroke occurred in 916 patients (9.0%)

in the ASA + ER DP group and 898 patients (8.8%) in the clopidogrel group [hazard ratio (HR) 1.01, 95% CI 0.92-1.11]. The hazard ratio was very close to 1.0 (equivalence) between the two antiplatelet regimens, but since the upper limit of the 95% CI exceeded the protocol-specified non-inferiority margin of 1.075; therefore, formal statistical non-inferiority of ASA + ER DP vs. clopidogrel could not be established.[3, 4]

Across multiple pre-specified and exploratory baseline subgroups, the relative difference between ASA + ER DP and clopidogrel for the primary outcome of first recurrent stroke was also consistent.[3] For the on-treatment analysis of the primary outcome, the results were [ASA + ER DP 777 (7.7%) recurrent strokes vs. clopidogrel 777 (7.7%); HR 1.07, 95% CI 0.97-1.18]. [3]

In further exploratory analyses of the main secondary endpoint of the composite of stroke, myocardial infarction or vascular death, ASA + ER DP and clopidogrel showed similar outcomes [(n=1333), 13.1% ASA + ER DP, vs. (n=1333), 13.1% clopidogrel; HR 0.99, 95% CI 0.92-1.07, p=0.83].[3, 4]

The rates of most tertiary efficacy outcomes were similar with the two agents, although the rate of new or worsening congestive heart failure was significantly lower in the ASA + ER DP group compared to clopidogrel [144 (1.4%) vs. 182 (1.8%); HR 0.78, 95% CI 0.62-0.96].[3]

As stated above, other regimens in PRoFESS investigated whether telmisartan, combined with ASA + ER DP or clopidogrel, would further reduce the risk of recurrent stroke. Initiation of blood pressure lowering with telmisartan after a stroke, with a relatively short duration of therapy of 2.5 years, did not significantly lower the rate of stroke or other major vascular events compared to placebo, according to results from PRoFESS. There was no significant difference in the number of patients with stroke in the telmisartan group compared to the placebo group (8.7% vs. 9.2%, respectively; hazard ratio [HR] 0.95, 95% confidence interval [CI] 0.86-1.04, p=0.23). Thus, the primary endpoint of superiority of telmisartan versus placebo could not be statistically confirmed. The mean follow-up period was 2.5 years, and it is unclear whether a longer follow-up period would have yielded statistical significance.[4]

Exploratory analyses with telmisartan suggested that there was no difference in the rates of recurrent stroke or major vascular events in the first 6 months of the trial (number of strokes: telmisartan 3.4% vs. placebo 3.2%; HR 1.07, 95% CI 0.92-1.25, p=0.38; major vascular events: telmisartan 4.7% vs. placebo 4.3%; HR 1.10, 95% CI 0.97-1.26, p=0.14). However, beyond 6 months the number of events were lower in the telmisartan group (number of strokes: telmisartan 5.3% vs. placebo 6.0%; HR 0.88, 95% CI 0.78-0.99, p=0.029; major vascular events: telmisartan 8.8% vs. placebo 10.1%; HR 0.87, CI 0.80-0.95, p=0.0029).[4]

Also, there was no significant reduction in two secondary telmisartan arm outcomes: 1) major vascular events (cardiovascular death, myocardial infarction, stroke and new or worsening heart failure) with telmisartan compared to placebo (13.5% vs. 14.4%, respectively; HR 0.94, 95% CI 0.87-1.01, p=0.11) or 2) rate of new diabetes mellitus (125 in the telmisartan group and 151 in the placebo group; HR 0.82, 95% CI 0.65 to 1.04, p=0.10).[4]

As stated above, functional outcome after a recurrent stroke was evaluated during PRoFESS using the modified Rankin scale, and the Barthel index 3 months after the stroke. The PRoFESS results showed that the functional outcome of recurrent stroke is similar in patients who receive ASA + ER DP compared with clopidogrel, or telmisartan compared with placebo. There was also no difference between these treatment groups for cognitive function in patients with recurrent stroke. Similar results were observed with the Barthel Index for all the treatment groups. Also, no difference was observed among the treatment groups with respect to the proportion of patients who were cognitively impaired (Mini Mental State Examination ≤24). Overall, approximately 18%, 14%, and 15% were cognitively impaired at 1 month, 2 years, and at the next to last study visit, respectively.[4]

Safety Results:

In PRoFESS, recurrent ischemic strokes occurred in 7.7% of patients in the ASA + ER DP group compared to 7.9 % in the clopidogrel group. Although there were 25 fewer ischemic stroke recurrences in the ASA + ER DP group

compared to clopidogrel, 5 more other/unknown strokes and 38 more hemorrhagic strokes were found in the ASA + ER DP group.[3, 4]

Despite the greater number of hemorrhagic strokes in the ASA + ER DP group, the number of individuals with fatal or disabling strokes (defined by a modified Rankin scale ≥ 3 at 3-months post-recurrent stroke) was similar in the two groups with 413 (4.1%) in the ASA + ER DP group, and 392 (3.9%) in the clopidogrel group [HR 1.05, 95% CI 0.96-1.16].[3]

Major hemorrhagic events occurred more frequently in the ASA + ER DP group (major hemorrhagic events: (419, 4.1%) compared to clopidogrel alone (365, 3.6%); HR 1.15, 95% CI 1.00-1.32, p=0.06). [3, 4]

Intracranial hemorrhages were a subset of major hemorrhagic events. The overall incidence of intracranial hemorrhage (including the 128 hemorrhagic strokes counted in the primary outcome) was higher in the ASA + ER DP group (1.4%) than in the clopidogrel group (1.0%) resulting in a HR of 1.42 (95% CI 1.11, 1.83, p=0.006). The difference between the treatment groups resulted mainly from the higher incidence of hemorrhagic strokes in the ASA + ER DP group.[3, 4]

The benefit-risk ratio expressed as the rate of recurrent stroke or major hemorrhagic event was not significantly different between ASA + ER DP and clopidogrel [ASA + ER DP 1194 (11.7%) vs. clopidogrel 1156 (11.4%); HR 1.03, 95% CI 0.95-1.11, p=0.50]. The total number of deaths in the study were 739 (7.3%) in the ASA + ER DP group, and 756 (7.4%) for clopidogrel.[3, 4]

The ASA + ER DP group had significantly more frequent premature discontinuations from study drug (2961, 29%), compared to clopidogrel (2290, 23%; p<0.001). Also, the ASA + ER DP group had a higher rate of adverse events leading to permanent discontinuation of study drug compared to clopidogrel [1650 (16.4%) vs. 1069 (10.6%)]. Further, permanent discontinuation from the ASA + ER DP group, because of headache was more common (593, 5.9%) compared to clopidogrel (87, 0.9%).[3]

In summary, the PRoFESS trial did not meet the pre-defined criteria for non-inferiority, but demonstrated similar rates of recurrent strokes with ASA + ER DP and clopidogrel. PRoFESS shows no evidence that either ASA + ER DP or clopidogrel was superior to the other in prevention of recurrent stroke.[3]

References:

1. Diener HC., et al. Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: the Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS). *Cerebrovascular Diseases* 2007; 23(5-6):368-80, 2007.
2. Diener P.H.-C., et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): Randomised, double-blind, placebo-controlled trial. *Lancet* 2004; 364(9431): 331-337.
3. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008; 359:1238-1251.
4. Diener HC, et al. European Stroke Conference, Nice, France, 14 May 2008.
5. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996; 143:1-13.

Headache Incidence and Management for AGGRENOX

Headache Incidence and Development of Tolerance

Both dipyridamole and aspirin have been available and widely used in the United States for more than thirty years and one-hundred years, respectively and have well established clinical safety profiles. Adverse events expected to occur during therapy with AGGRENOX would be those adverse events already known to occur with its components, dipyridamole and aspirin.

The European Stroke Prevention Study 2 (ESPS-2) confirmed the efficacy and safety of dipyridamole and aspirin alone and in combination in the prevention of fatal and non-fatal stroke in patients who had transient ischemia of the brain or ischemic stroke (data on file). All 6,602 patients in ESPS-2 were evaluated for safety at one month, three months and every three months thereafter for the two-year duration of the study. Safety evaluations consisted of adverse event monitoring, laboratory examinations and blood pressure measurements.

Headache was one of ten adverse events with an incidence $\geq$1% in the AGGRENOX treatment group compared to placebo. The overall incidence of headache in the ESPS-2 study was 39.2% with AGGRENOX, 38.3% with extended release dipyridamole 200 mg alone, 33.8% with immediate release aspirin 25 mg alone and 32.9% with placebo. Reported episodes of headache were usually transient. The incidence of headache in the AGGRENOX treatment group declined from 25% at the one-month follow-up safety evaluation, to 14% by the three-month evaluation, an incidence only 1% greater than reported in the placebo treatment group. By the six-month evaluation, the incidence of headache in the AGGRENOX treatment group was 11%, equal to the incidence reported in the placebo group (data on file).

The rapid development of tolerance to dipyridamole associated headache with AGGRENOX was also evaluated in a randomized bioequivalency trial (Theis JGW et al. Br J Clin Pharmacol. 1999;48:750-5). In this study, transient headache episodes of mild intensity were reported by 67% of young, healthy volunteers on Day 1 of a 5.5 day treatment period of AGGRENOX administered twice daily. By days 2-4, the incidence of headache declined to 31-37%. A further reduction in headache incidence to 24% was reported on Day 1 of the second 5.5 day treatment period (Day 8 overall), with a continuing decline reported over the next three days to 3-12%. Reports of headache peaked 2-3 hours after administration of the morning dose, coinciding with peak plasma concentrations of dipyridamole. Discontinuation of therapy due to headache was reported by 8% of patients. This study concluded that counseling patients about the possible occurrence of headache and the rapid development of tolerance with AGGRENOX may reduce early treatment withdrawals and increase patient compliance.

Headache Management

A study was conducted to assess the prevalence of headache after administration of a single dose of AGGRENOX, and the efficacy of acetaminophen 1000 mg versus placebo in treating the headache associated with AGGRENOX (Lipton RB et al. Neurology. 2004;63:1099-1101). During the acute treatment phase of this study, healthy adults, 55 years of age or older (n = 513) received a single dose of AGGRENOX. Patients who developed headaches within two hours were randomized to receive acetaminophen 1000 mg or placebo. The primary efficacy endpoint for the acute treatment phase was the reduction from moderate or severe headache to mild or no headache within two hours after AGGRENOX dosing. Secondary endpoints included post-medication self-assessment of pain intensity, global self-assessment of AGGRENOX therapy, and tolerability assessments.

Patients who developed AGGRENOX associated headaches in the acute phase were eligible to enroll into the pre-emptive phase of this study. For seven days, patients received acetaminophen 1000 mg (n = 99) or placebo (n = 100) twice daily, followed by AGGRENOX capsules. The primary efficacy endpoint for the pre-emptive phase was reduction in the frequency of moderate or severe headache. Secondary endpoints included global assessment of headache severity, impression of rescue medication two hours after AGGRENOX dosing, and tolerability assessments.

During the acute treatment phase, 204 (39.7%) of the study participants developed a moderate to severe headache after administration of a single dose of AGGRENOX. Headache was reported more often by women (49.6%) than men (28.6%) [$p < 0.0001$]. Ethnic differences in the frequency of headache were also noted, with Hispanics (76.8%)

reporting headaches more frequently than Whites (31.8%) and African Americans (5.8%) respectively [p<0.0001]. No significant differences were identified for age. Non-significant differences were also observed in pain intensity ratings at one, two and four hours after treatment and headache response, defined as reduction from moderate or severe headache to mild or no headache within two hours, in acetaminophen-treated (75.5%) and placebo-treated patients (69.4%).

During the pre-emptive phase, placebo-treated patients reported moderate to severe headache on 237 days (20.3% of possible days) compared to 262 days (21.8% of possible days) in acetaminophen-treated patients. Headache was reported on Day One by 41.2% of the participants receiving placebo and 48.8% of the participants receiving acetaminophen, respectively. The frequency of headaches reported on Day Seven decreased significantly to 17.1% of placebo-treated patients and 18.6% of acetaminophen-treated patients [p<0.001, x^2] for trend. No significant differences were observed between treatment groups for any of the secondary endpoints.

The findings of this study regarding the incidence of headache and the self-limiting nature of headache with AGGRENOX therapy are consistent with ESPS-2 and prior literature. Acetaminophen was not found to be more effective than placebo in treating headaches following AGGRENOX dosing or preventing headaches prior to AGGRENOX dosing. However, due to the self-limiting nature of AGGRENOX headaches and the high placebo response, demonstration of superiority for any headache treatment would be very difficult.

Dose Titration for AGGRENOX

Boehringer Ingelheim Pharmaceuticals Inc. has conducted several studies to understand the nature of dipyridamole-induced headaches and to evaluate strategies to decrease the incidence of the headaches associated with AGGRENOX.

The Dosage and Administration section of the AGGRENOX Prescribing Information has been updated with the addition of an alternative dosing regimen:

> *Alternative Regimen in Case of Intolerable Headaches:*
>
> *In the event of intolerable headaches during initial treatment, switch to one capsule at bedtime and low-dose aspirin in the morning. Because there are no outcome data with this regimen and headaches become less of a problem as treatment continues, patients should return to the usual regimen as soon as possible, usually within one week.* [1]

Available data indicate that moderate to severe headaches can occur after the first dose of AGGRENOX in a subset of patients who are sensitive to dipyridamole. This subset is estimated to include fewer than 50% of the AGGRENOX patient population. In sensitive subjects who develop a moderate/severe headache following a first dose of AGGRENOX, the incidence of headache can be expected to decrease over time, leveling off after approximately 5 days of AGGRENOX twice daily treatment.[2] In a randomized, double-blind, placebo-controlled, parallel group study, the frequency of dipyridamole-induced headache was reduced when AGGRENOX treatment was initiated with once daily dosing compared to standard twice daily dosing. The intensity of the dipyridamole-induced headaches was not reduced with an AGGRENOX titration regimen, however. Exploratory evaluations with data from this study further suggest that the proportion of patients reporting any grade of headache for the first 10 days of AGGRENOX twice daily treatment was considerably less if the patient initiated treatment with AGGRENOX once daily dosing than with standard twice daily dosing.[3]

The data from ESPS-2 (European Stroke Prevention Study 2) suggest that AGGRENOX administered twice daily and low-dose aspirin administered twice daily, act similarly in reducing the risk of secondary stroke during the first weeks of treatment. An alternative short-term dosing regimen which would allow for AGGRENOX once daily

dosing at bedtime together with the administration of low dose aspirin in the morning during initial treatment with AGGRENOX is expected to provide similar protection against stroke as standard AGGRENOX therapy for those patients who experience intolerable headaches when starting AGGRENOX therapy.[4]

References:

1. Aggrenox® (aspirin/extended-release dipyridamole) 25 mg/200 mg capsules [product information]. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals Inc., January 31, 2007.
2. Lipton RB et al. Acetaminophen in the treatment of headaches associated with dipyridamole-aspirin combination. *Neurology*. 2004;63:1099-1101.
3. Chang YJ et al. Dose titration to reduce dipyridamole-related headache. *Cerebrovasc Dis.* 2006;22:258-62.
4. Data on File.

DOMINION Results

Impulse control disorders (ICDs) have been identified as a significant clinical malady in Parkinson's disease (PD).[1-8] ICDs refer to a variety of disorders that involve a patient's inability to resist gratifying potentially deleterious or inappropriate behaviors. The National Gambling Impact Study Commission (NGISC) Final Report issued in 1999 estimated that the annual prevalence of both pathological and problem gambling behavior is approximately 1.3-2.9% in the US adult population.[9] Other prevalence estimates are 5% for compulsive sexual behavior, and 1-3% for binge-eating disorder.[10,11] Preliminary prevalence estimates for ICDs reported in PD from formal assessment studies are 1.7-6% for pathological or problem gambling, 2-10% for compulsive sexual behavior, and 0.4-1.5% for compulsive buying.[1-8] Some publications have implicated dopaminergic medications including levodopa and dopamine agonists (DAs) as contributory to ICD incidence, however, they have been small sample sizes.

Objectives/Study Design[1]:

DOMINION was a cross-sectional, retrospective screening and case-control study that examined the frequency of, and risk factors associated with, impulse control **d**is**o**rder in Parkinson's disease patients treated with **MI**RAPEX a**n**d other ant**i**-parkins**on** agents.

The primary objective of this study was to determine whether the frequency of current ICDs (having occurred in the previous 6 months), including either problem or pathological gambling, compulsive sexual behavior, compulsive buying, or binge-eating, was equivalent in PD patients currently treated with MIRAPEX (pramipexole dihydrochloride tablets) compared with non- DAs. The cross-sectional part of the study, Visit 1, included all subjects entered into the study and assessed this primary endpoint.

A secondary objective of this study was to explore risk factors (including treatment exposure and psychiatric/neuropsychological functioning) which may distinguish PD patients with a current ICD from matched control patients without a current or past (since PD onset) ICD. This objective was addressed via the case-control part of the study, Visit 2, which included all patients identified as having a current ICD, and an equal number of matched control patients. Additional secondary objectives assessed in the cross-sectional, retrospective screening component of the study included:

- Whether the frequency of current ICD is equivalent in PD patients currently treated with a DA compared to other anti-parkinson medications (i.e., levodopa).
- Whether the frequency of past (since PD onset) ICDs is equivalent in PD patients treated with MIRAPEX compared with non-DAs at the time of ICD onset.
- Whether the frequency of past ICDs is equivalent in PD patients treated with a DA agonist compared to other anti-parkinson medications (i.e., levodopa) at the time of ICD onset.

Endpoints[1]:

Primary endpoints:

The primary endpoint assessed in the cross-sectional, retrospective screening component of the study was the occurrence of a current (past six months) ICD as assessed using the following instruments. A positive identification of a current ICD on any 1 or more of these instruments identified the subject as having a current ICD.

- Problem/pathological gambling: Modified Massachusetts Gambling Screen (MAGS).
- Compulsive sexual behavior: Modified Minnesota Impulsive Disorder Interview (MIDI) for Sexuality.
- Compulsive buying: Modified Minnesota Impulsive Disorder Interview (MIDI) for Compulsive Buying
- Binge- eating: DSM-IV binge-eating research criteria questionnaire.

Secondary endpoints:

Secondary endpoints derived from the cross-sectional, retrospective screening part of the study include:

- The occurrence of a current (previous 6 months) ICD. The anti-parkinson medication(s) correlated with the ICD was the anti-parkinson medications taken by the subject at that time.
- The occurrence of a past (since onset of PD) ICD. The anti-parkinson medication(s) associated with the ICD was the anti-parkinson medications taken by the subject at the time the ICD began.

Secondary endpoints analyzed from the case-control part of the study include:

- Various demographic and medical history measures, including anti-parkinson agent treatment exposure (from detailed medical history), duration of PD, lifetime ICD history, South Oaks Gambling Screen (SOGS), and severity of PD (from Unified Parkinson Disease Rating Scale; UPDRS).
- Scores on psychiatric/neuropsychological function as measured using the following psychiatric/neuropsychological instruments/tests:
  - Montreal Cognitive Assessment (MoCA)
  - Geriatric Depression Scale (GDS)
  - State-Trait Anxiety Inventory (STAI)
  - Obsessive-Compulsive Inventory – Revised (OCI-R)
  - Alcohol Use Disorders Identification Test (AUDIT)
  - Temperament and Character Inventory (TCI) Novelty Seeking
  - Altman Self-Rating Scale for Mania (ASRM)
  - Barratt Impulsiveness Scale (BIS-11)
  - Delayed Discounting Task

Subjects:

Inclusion criteria:

1. Male or female outpatients, aged 30 to 75 years of age, with idiopathic PD previously confirmed by at least two of the following signs: resting tremor, bradykinesia, rigidity. Patients were recruited for study participation in the context of routine clinical care based on a prospective, site-specific, documented recruitment plans designed to minimize selection bias.
2. Patients must have been treated with anti-parkinson medication for a period of 1 year or greater. Patients must have demonstrated a treatment response, in the opinion of the Investigator.
3. Patients' use of a DA must have been stable for the previous 6 months. That is, patients must not have started any new DA medication in the previous 6 months or stopped taking any previously-used DA medication within the past 6 months. Changes in dosage are acceptable.
4. Patients must be willing and able to comply with study procedures.
5. Patients must be willing and able to give meaningful, written informed consent. This must be completed prior to beginning any study procedures, in accordance with GCP and local legislation.

Exclusion criteria:

1. Atypical PD due to drugs, metabolic disorders, encephalitis, trauma, or other neurodegenerative diseases.
2. Significant cognitive impairment which, in the opinion of the Investigator, would interfere with the ability to complete all the tests required in the protocol.
3. Participation in another clinical trial within the past 2 months.

Assessment and Analyses[1]:

Subjects were assessed for a current (past 6 months) ICD using a modified Massachusetts Gambling Screen (MAGS)[12] for problem/pathological gambling, a modified Minnesota Impulsive Disorders Interview (MIDI)[13] for compulsive sexual behavior and buying, and DSM-IV[14] research criteria for binge-eating disorder. Demographic and clinical data were obtained from each patient and verified by chart reviews when needed. Odds ratios with 95% confidence intervals were calculated and a Cochran-Mantel-Haenszel test was performed for comparing of ICD frequencies in DA- versus non-DA- treated groups and MIRAPEX- versus ropinirole-treated groups. Variables that were independently associated with ICDs were further entered into a logistic regression analysis. Levodopa equivalent daily dosages (LEDDs) for analyses were calculated using the following conversion factors: 100mg levodopa = 133.3mg controlled release levodopa = 80mg levodopa + catechol-O-methyl-transferase inhibitor = 1mg pergolide = 1mg MIRAPEX = 4mg ropinirole.

Efficacy Results[1]:

A total of 3090 patients (64.1% male; mean age = 63.8 years) at 46 sites in the United States (n=33) and Canada (n=13) completed the initial cross-sectional component of the study. Two-thirds (66%; n=2040) of the subjects were on a DA agonist with 41.6% (n=1286) on MIRAPEX, 21.1% (n=651) on ropinirole, and 1.6% (n=50) on pergolide as their only DA. Of these patients, 82.9% were also taking levodopa. Almost all patients not on a DA, 94.4% (n=991) were taking some form of levodopa with overall levodopa use of 86.8%. Most patients, 52.6%, were < 65 years of age. In this component of the study, patients with current ICDs had a college degree or higher compared to patients without a current ICD (51.3% compared to 56.2%) and were about 4 years younger on average within the < 65 year age group (49.5% compared to 71.9%). The median LEDD was 600mg in patients without current ICDs compared to a median of 750mg in patients with current ICDs. In the MIRAPEX vs. other single DAs evaluation, patients with a current ICD were younger in both subgroups, with no difference in gender or age overall and within subgroups. Current ICD patients were younger in both groups in the DA versus non DA evaluation. A higher percentage of patients with a current ICD were associated with both a higher percent of male patients and a higher Hoehn & Yahr stage in the non DA subgroup.

One or more current ICDs were identified in 13.6% of patients. One ICD was present in 8.7% of patients and 4.9% had 2 or more ICDs. The frequencies of the single ICDs were compulsive buying (5.7%), problem/pathological gambling (5%), binge-eating disorder (4.3%), and compulsive sexual behavior (3.5%).

ICDs as a group were more common in DA-treated than non DA-treated patients (17.1% versus 6.9%, respectively; odds ratio [95% CI] =2.72 [2.08,3.54], P<0.001). This same pattern was seen across all of the ICDs evaluated. Overall ICD frequencies for DA treatment alone versus DA plus levodopa treatment was similar (14.2% vs. 17.6%, respectively; P=0.12).

Among individual DAs, there was no statistically significant difference in overall ICD frequency for MIRAPEX- and ropinirole-treated patients (17.7% vs. 15.5%, respectively; odds ratio [95% CI] =1.22[0.94,1.57], P=0.14). This finding was seen across all of the ICDs evaluated.

In DA-treated patients, the most common ICD was compulsive buying (7.2%), followed by problem/pathological gambling (6.4%), binge-eating (5.6%), and compulsive sexual behavior (4.4%). Pathological gambling alone was 3.5%.

In the case-control component, 59.6% of patients with an education level of college graduate and above were without a current ICD compared to 55.7% of those with an ICD. As was seen in the cross-sectional component, there was no significant difference between patients with and without a current ICD with regard to race. Patients without a current ICD were about 6 months older than patients with a current ICD. Patients on a DA were younger (<65 years: 70.3%

vs. 58.3%) and the median duration of PD was 6.9 years compared to 6.0 years for patients not on a DA. In patients without a current ICD, the mean duration of PD was 6 months less than in patients with a current ICD.

Logistic regression showed that ICD patients were slightly younger (mean age = 60.2 vs. 64.4 years, respectively; P<0.001), less likely to be married, on higher LEDD, and were more likely to have a self-reported family history of gambling problems (7.1% vs. 3.6%, respectively; P<0.001) than non-ICD patients; there were no between-group differences in gender (P=0.71) or disease severity as measured by Hoehn and Yahr stage (P=0.93).

There was a 2 to 3 fold increased risk of an ICD in the age group less than 65 years and in patients that used a DA. Being single and using levodopa increased the risk 1.5 to 2 fold. Age, family history of gambling, and DA dose were associated with a higher risk, i.e. having an odds ratio >2. Being single and levodopa dose were associated with a lower risk, i.e. having an odds ratio between 1 and 2. An independent association with the presence of an ICD was seen with both higher DA doses and levodopa LEDDs (all P-values <0.01).

When comparing MIRAPEX with other single DA treatments there was no statistically significant difference found in the proportion of overall past ICDs (21.3% vs. 20.1%). A statistically significant difference was found when DA and non DA treatments were compared (22.0% vs. 7.2%), however the interpretation of past ICDs was non-conclusive.

The following are the result of correlation analyses for the psychiatric / neuropsychological instruments assessed in the case-control component of the study:

MoCA
The MoCA score showed no discrimination between 'current ICD' and 'no current ICD' patients.

UPDRS
There was a trend (P=0.0527) for the UPDRS total score to discriminate between 'current ICD' and 'no current ICD' patients. The difference in patients with a current ICD versus patients with no current ICD was observed in UPDRS Parts I (P<0.0001), II (P<0.0001) and IV (P=0.0022), but not in UPDRS Part III (P=0.7016).

GDS
The values for the GDS above the median were statistically significant in the percentage of patients with a current ICD (71.3% vs. 45.0%).

STAI
STAI-state (P=0.0340) and STAI-trait (P=0.0129) subscales values above the median were statistically significant in the percentage of patients with no current ICDs (57.7% and 60.8%, respectively).

OCI-R
The OCI-R values above the median were statistically significantly higher in the percentage of patients with a current ICD (66.2% vs. 36.8%).

ASRM
There was a statistically significant difference in the number of patients below and above the median of this scale for mania (P=0.0442).

AUDIT, TCI, BIS-11, and DDT
These test results showed no discrimination between patients having a current ICD and patients not having a current ICD.

SOGS

For current gambling, the mean SOGS value in patients with a current ICD was 10 times larger compared to patients with no current ICDs. In SOGS for past gambling, the score was still 8 times higher in patients from the group with a current ICD. Overall, a total of 26 (9.2%) of patients were described as having current problem gambling and 73 (25.8%) as having current pathological gambling. Patients classified as having past gambling experiences (anytime since PD onset) showed an overall of 28 (9.9%) of past problem gamblers and 89 (31.4%) of past pathological gamblers.

In the full population of patients with and without a current ICD, rank correlations (according to Spearman) were calculated. High correlation was found for OCI-R and GDS (r=0.42), followed by OCI-R and TCI (r=-0.39), STAI-trait and STAI-state (r=0.38), GDS and UPDRS total score (r=0.36), and GDS and TCI (r=0.32). All these correlations were statistically significant (P<0.0001).

A logistic regression for overall ICDs in the case-control component of the study identified eight variables: family history of gambling, marital status, UPDRS Part II, GDS, STAI-Trait, OCI-R, TCI, and ASRM. A logistic regression analysis of each of the individual ICDs (restricted to patients with a specific single ICD) revealed the following statistically significant variables. For current gambling, 4 variables were found: UPDRS Part II, GDS, STAI-Trait and OCI-R. For current compulsive sexual behavior, 5 variables were found: UPDRS Part I, GDS, OCI-R, TCI, and ASRM. For current compulsive buying behavior, 7 variables were found: marital status (being married), UPDRS Parts II & III, GDS, OCI-R, TCI, and ASRM. For binge eating, 5 variables were found: family history of gambling problems, UPDRS Part II, GDS, OCI-R, and ASRM.

Safety Results[1]:

The median extent of exposure (in weeks) for dopamine agonist and levodopa-treated patients with and without any current or past ICD was evaluated. Patients with a current ICD taking MIRAPEX, pergolide, or multiple DAs showed a higher median treatment exposure than patients without a current ICD. Patients on ropinirole had similar durations of exposure in patients with and without a current ICD. Patients with a current ICD on levodopa alone or ‘a single DA + levodopa’ had a lower treatment exposure.

As observed in patients with a current ICD, patients with a past ICD taking MIRAPEX, pergolide, or multiple DAs showed a higher median treatment exposure than patients without a past ICD. Patients on ropinirole had similar treatment exposure in both groups. Patients on levodopa only had a lower median treatment duration exposure.

In this study there were no deaths, and a total of 26 adverse events (see Table 1 below), including seven SAEs overall. Of the SAEs reported in this study, none were considered to be related to pramipexole or other anti-parkinson medication by the investigator or the clinical monitor.

Table 1 Adverse event overall summary – cross-sectional component
Treatment analysis: Current ICD - Overall

ICD (%)	No current N	Current ICD N (%)	Total N (%)
Number of patients	2670 (100.0)	420 (100.0)	3090 (100.0)
Patients with any AE	7 (0.3)	9 (2.1)	16 (0.5)
Patients with severe AEs	1 (0.0)	3 (0.7)	4 (0.1)
Patients with investigator defined drug-related AEs	0 (0.0)	0 (0.0)	0 (0.0)
Patients with other significant AEs (per ICH E3)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with AEs leading to discontinuation of trial drug	0 (0.0)	0 (0.0)	0 (0.0)
Patients with significant AEs (pre-specified events)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with serious AEs	2 (0.1)	2 (0.5)	4 (0.1)

Fatal	0 (0.0)	0 (0.0)	0 (0.0)
Immediately life-threatening	0 (0.0)	1 (0.2)	1 (0.0)
Disability / incapacitating	0 (0.0)	0 (0.0)	0 (0.0)
Required hospitalization	2 (0.1)	2 (0.5)	4 (0.1)
Prolonged hospitalization	0 (0.0)	1 (0.2)	1 (0.0)
Congenital anomaly	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

A patient may appear in more than one seriousness criterion.

Percentages are calculated using total number of patients per treatment as the denominator.

MedDRA version 11.0 was used for reporting; ICD= Impulse Control Disorder; AEs=Adverse Events

Conclusions[1]:

The results of this observational study show that the odds of having at least one of the four commonly reported ICDs in PD was two- to three-times higher in the DA-treated group compared with the non DA-treated group, a finding which applied to each of the ICDs assessed. The higher odds appear to represent a class, rather than a specific medication finding and were consistent across all of the ICDs evaluated in the study. Although previous research in PD has focused on compulsive gambling, as was seen in this study, a broader range of ICDs is observed in PD patients. The following may be independent risk factors for ICD development in PD patients:

- Young age
- DA treatment and higher DA dose
- Levodopa treatment and higher levodopa dose
- Marital status of single
- Family history of gambling behavior
- Living in the United States

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Calm-PD Study (Mirapex vs Levodopa)

CALM – PD STUDY

Summary

The option of initial treatment with pramipexole versus levodopa in 301 patients with early Parkinson's disease (PD) in relation to development of dopaminergic motor populations was studied at 2 years and again at 4 years.

The original 2 year trial report showed that 28% of patients assigned to pramipexole developed dopaminergic complications versus 51% assigned to levodopa ($p < .001$) and the mean improvement in total UPDRS score was greater in those assigned to levodopa compared with pramipexole (9.2 versus 4.5 units, $p < 0.001$). At 4 years, 52% of subjects assigned to initial pramipexole treatment reached the primary endpoint compared with 74% in the levodopa group ($p< 0.0001$). The percentage of subjects experiencing specific dopaminergic complications (pramipexole versus levodopa) were dyskinesias (25% versus 54%; $p < 0.0001$), wearing off (47% versus 63%; $p = 0.015$), on-off fluctuations (7% versus 8%; $p = 0.34$). The mean improvement in total UPDRS scores from baseline to 48 months was greater in the levodopa group than in the pramipexole group (3.6 versus – 0.98 units; $p< 0.01$). The authors concluded that in patients with early PD, initial treatment with pramipexole compared with levodopa, reduced the 4-year risk of developing a dopaminergic motor complication by about 30% including a > 50% reduction in dyskinesias. Despite the opportunity for supplementation with open-label levodopa in both treatment groups, subjects assigned initially to levodopa showed greater improvement in total UPDRS than subjects assigned initially to pramipexole. Five year results are presented.

Two-Year Data

This study compared the option of initial treatment with pramipexole versus levodopa in patients with early Parkinson's disease (PD) with regard to the development of dopaminergic motor complications including wearing-off, on-off motor fluctuations, and dyskinesias.[1-4] Up to this time, there has been no controlled evaluation of the long-term consequences of initiating dopaminergic therapy with pramipexole versus levodopa. The primary study objective was to assess the outcomes of a strategy to initiate pramipexole treatment compared with levodopa treatment in early PD regarding development of dopaminergic motor complications. A secondary study objective was to measure the rate of dopamine transporter loss via single-photon emission computerized tomography (SPECT) brain imaging. This study represents comparing pramipexole with levodopa in early Parkinson's Disease, Comparison of the Pramipexole versus levodopa in Parkinson's Disease (CALM-PD) 2 year preliminary results. Time to the first occurrence of any of 3 dopaminergic complications (wearing off, dyskinesias, or on-off motor fluctuations); changes in scores on the Unified Parkinson's Disease Rating Scale (UPDRS), assessed at baseline and follow-up evaluations; and, in a subgroup of 82 subjects evaluated at baseline and 23.5 months, ratio of specific to nondisplaceable striatal ^{123}I 2 β carboxymethoxy - 3 β - (4-iodophenyl) tropane (β-CIT) uptake on single photon emission computed tomography imaging of the dopamine transporter.[3]

Inclusion and Exclusion Criteria:

Eligible subjects were adults aged 30 years or older who had idiopathic PD for fewer than 7 years and who required dopaminergic antiparkinsonian therapy at the time of enrollment. Patients who had taken levodopa or a dopaminergic agonist in the 2 months prior to enrollment were excluded. Subjects were required to be in Hoehn and Yahr stage I, II, or III, a scale that classifies PD into 5 clinical stages ranging from mild unilateral (stage I) to severe, bed-bound illness (stage V). Subjects were excluded if they had (1) =history of a previous dopaminergic

complication, (2) atypical parkinsonian syndromes, (3) serious concurrent illness, (4) treatment with methylphenidate, cinnarizine, reserpine, amphetamine, or monoamine oxidase type A inhibitors in the past 3 months, (5) treatment with pramipexole in the past 4 months, (6) treatment with neuroleptics, metoclopramide, alphamethyldopa, or flunarizine in the past 6 months, or (7) an unstable dosage of selegiline, amantadine, anticholinergic therapy, or other central nervous system active therapies (eg, hypnotics, antidepressants, anxiolytics) in the past 2 months.

Early PD patients (n=301) who were at the point of requiring dopaminergic therapy to treat emerging disability were randomized in a parallel, multicenter (22 U.S. and Canadian sites), double-blind fashion to (a) active pramipexole and placebo levodopa or (b) placebo-pramipexole and active levodopa.[1,2] Subjects were followed prospectively at 22 movement disorder centers for 23.5 months. During the first 10 weeks, subjects were permitted in a blinded fashion to adjust experimental therapy to treat residual disability to one of three daily dosage levels, either: (a) 1.5 mg, 3.0 mg or 4.5 mg pramipexole, or (b) 75/300 mg, 112.5/450 mg or 150/600 mg carbidopa/levodopa. From week 11 to month 23.5, investigators were allowed to add open-label levodopa to treat continuing or emerging disability. The prespecified primary endpoint was the time to first occurrence of wearing off, on-off effects, dyskinesias (dopaminergic complications). The Unified Parkinson's Disease Rating Scale (UPDRS) was assessed at baseline and follow-up evaluations. At baseline, groups were balanced for age (mean 61 yrs), gender (65% male), time since diagnosis (1.6 yrs), and mean total UPDRS score (32 units). Initial pramipexole treatment resulted in significantly less development of wearing off, dyskinesias, or on-off motor fluctuations (28%) compared with levodopa (51%) (hazard ratio 0.44, $p<0.0001$).[4] The proportion of subjects experiencing specific dopaminergic complications (pramipexole vs. levodopa; hazard ratios, 95%, p-value) were: wearing off (24% vs. 38%; p=0.009), dyskinesias (10% vs. 31%, p=0.07). In the pramipexole group 48% required supplemental levodopa compared with 36% in the levodopa group (hazard ratio 1.49, p=0.03). The mean improvement in total UPDRS scores from baseline to 23.5 months was greater (p=0.0002) in the levodopa group (31.1 to 21.9) than in the pramipexole group (32.5 to 28.1).[1]

Adverse Events

More patients in the pramipexole group experienced somnolence (P=.003), hallucinations (P=0.03), and both generalized (P=.01) and peripheral edema (P=.002) compared with those in the levodopa group. The differences in somnolence and hallucinations between the two groups emerged during the escalation phase of the trial, whereas the differences for edema emerged during the maintenance phase of the trial.[4] Three subjects reported falling asleep while driving, two of whom had been randomized to pramipexole and 1 to levodopa. None were taking open-label levodopa. Two of these events resulted in motor vehicle crashes, one in a subject randomized to levodopa and the other in a subject randomized to pramipexole. Two additional subjects complained of "abrupt" or "sudden onset" drowsiness unrelated to driving, both were allocated to pramipexole.

Conclusions

The authors concluded that pramipexole delayed the onset of dopaminergic motor complications compared with levodopa in patients with early PD.[1] Fewer patients receiving initial treatment for PD with pramipexole developed dopaminergic motor complications than with levodopa therapy. Despite supplementation with open-label levodopa in both groups, the levodopa-treated group had a greater improvement in total UPDRS compared with the pramipexole group.[4]

Four-Year Data

The four-year comparison outcomes of dopaminergic motor complications following initial treatment of early PD patients with pramipexole versus levodopa was studied.[5] The original 2 year trial report showed that 28% of patients assigned to pramipexole developed dopaminergic complications versus 51% assigned to levodopa ($p < 0.001$) and the mean improvement in total UPDRS score was greater in those assigned to levodopa compared with pramipexole (9.2 versus 4.5 units, $p < 0.001$).[4] This report extends the period of blinded, controlled observation to 4 years.[5] Early PD patients (n = 301) who had developed disability requiring dopaminergic therapy consented to be randomized in a double-blind fashion to pramipexole or levodopa. Subjects were followed for 48 months at 22 academic movement

disorder sites in the U.S. and Canada. During the initial 10 weeks following randomization, patients were allowed in a blinded fashion to adjust experimental therapy to treat residual disability to one of three dosage levels: a) 1.5 mg, 3.0 mg, or 4.5 mg pramipexole or b) 75/300 mg, 112.5/450 mg, or c) 150/600 mg carbidopa/levodopa. From week 11 to month 48, investigators were permitted to add open-label levodopa to treat continuing or emerging disability. Following month 24, subjects were also allowed to alter the dosage level of the original study medication. The prespecified primary outcome variable was the time to the first occurrence of any of three dopaminergic motor complications; dyskinesias, wearing off, on-off fluctuations. The UPDRS was assessed at baseline and follow-up evaluations. At 4 years, 52% of subjects assigned to initial pramipexole treatment reached the primary endpoint compared with 74% in the levodopa group, ($p < 0.0001$). The percentage of subjects experiencing specific dopaminergic complications (pramipexole versus levodopa) were dyskinesias (25% versus 54%; $p < 0.001$), wearing off (47% versus 63%; $p = 0.015$), on-off fluctuations (7% versus 8%; $p = 0.34$). The mean improvement in total UPDRS scores from baseline to 48 months was greater in the levodopa group than in the pramipexole group (3.6 versus - 0.98 units; $p < 0.01$).[5] The authors concluded that in patients with early PD, initial treatment with pramipexole compared with levodopa reduced the 4-year risk of developing dopaminergic motor complication by about 30% including a > 50% reduction in dyskinesias. Despite the opportunity for supplementation with open-label levodopa in both treatment groups, subjects assigned initially to levodopa showed greater improvement in total UPDRS than subjects assigned initially to pramipexole.[5]

Five-Year Data

The rate of nigrostriatal dopaminergic degeneration after initial treatment with pramipexole or levo-dopa in early PD was studied in 56 patients previously enrolled in the CALM-PD CIT study; 6 patients were imaged with [123I] β-CIT 58 months in a multicenter manner in U.S. and Canadian movement disorder clinics. These patients were initially randomly assigned to receive pramipexole 1.5-4.5 mg (n=42) or levodopa 300-600 mg. For patients with residual disability the dosage was escalated during the first 10 weeks and subsequently open label levodopa could be added. During the past year following completion of the CALM-PD study patients were treated as needed without any restrictions to their PD medications. The primary imaging outcome variable was the percent change from baseline in striatal [123I) β-CIT uptake after 58 months. [123I) β-CIT SPECT imaging was obtained 58 months after their baseline scan on 56 patients, 27 initially treated with L-dopa and 29 initially treated with pramipexole. SPECT imaging showed a decline in [123I) β-CIT striatal uptake from baseline of 25.2±12.6% at 58 months in the cohort. Comparison of patients based on the initial treatment group in the CALM-PD study showed that the percent loss in striatal [123I) β-CIT uptake from baseline was 21.3±13.4% in those patients initially treated with pramipexole compared to 29.3±10.6% in the group initially treated with levodopa (p=0.02). At 58 months 5/29 subjects remained of pramipexole alone without L-dopa treatment. Patients initially treated with pramipexole compared to L-dopa demonstrated a relative reduction in the rate of loss of striatal [123I) β-CIT uptake during a 58-month evaluation period (including 12 months of of unrestricted treatment with any PD medication). By 58 months 85% of subjects initially treated with pramipexole had been treated with L-dopa. The data cannot distinguish between a slowing of [123I) β-CIT loss from baseline due to pramipexole or an accelerated [123I) β-CIT loss due to L-dopa. Additional studies to further characterize the clinical follow-up on these patients are underway.[6]

CALM-CIT Study

The long-term [123I) β-CIT uptake in subjects enrolled in the ELLDOPA-CIT and CALM-CIT studies with baseline scans without evidence of dopaminergic deficit (SWEDD) was assessed.[7] [123I) β-CIT SPECT imaging was used to assess progressive dopamine transporter loss in PD in the CALM-PD and ELLDOPA studies. ELLDOPA-CIT assessed the effect of L-dopa vs placebo in untreated PD patients not requiring symptomatic medication, mean duration since diagnosis of 0.5 yrs (N=142) recruited from 31 sites. CALM-PD compared initial treatment with pramipexole and L-dopa in patients requiring dopaminergic therapy, mean duration since of diagnosis 1.5 yrs (n=82) recruited from 17 sites. All subjects had to show two of three of the cardinal features of PD, tremor, rigidity or bradykinesia. The primary imaging outcome was the striatal [123I) β-CIT update at baseline. Scans demonstrating <25% reduction in age adjusted putamen [123I) β-CIT uptake (compared to healthy subjects, N=74) were defined as SWEDD. In the ELLDOPA-CIT study 21/142 (14%) had a scan without evidence of dopamine transporter deficit

(SWEDD). Of these 21 subjects followed with sequential scans 19/19 at nine months and 17/17 at 18 months continued to demonstrate SWEDD. The mean (SD) striatal β-CIT uptake at baseline for the SWEDD was 5.53±1.17 (N=21) compared to 3.16±74 (N=121) for the scans with a β-CIT uptake deficit. In the CALM study 3/82 (4%) of subjects had a SWEDD at baseline and of those subjects, 3/3 had a SWEDD at 22 months. It was concluded that imaging clinical trials show 3-14% of enrolled subjects have SWEDD. The frequency of subjects with SWEDD may be increased in studies recruiting very early, minimally symptomatic PD. All SWEDD at baseline remained without dopaminergic deficit at 9-22 month follow-up. The data suggest that subjects with baseline SWEDD may be identified as a distinct population within a clinical trial. Current study is underway to further evaluate the clinical symptoms, progression of disease, and final diagnosis to better characterize those subjects with SWEDD.[7]

Six-Year Data[7]

The primary outcome variable was the time-weighted average of self-reported disability scores in the "on" and "off" states as measured by the Schwab and England Activities of Daily Living Scale at the final visit. Secondary outcomes included the Unified Parkinson's Disease Rating Scale score, the presence and severity of dopaminergic motor complications, quality-of-life scale scores, Geriatric Depression Scale score, Epworth Sleepiness Scale score, and adverse events.

After a mean (SD) follow-up of 6.0 (0.2) years, mean (SD) self-reported weighted Schwab and England Activities of Daily Living Scale scores were similar in the initial pramipexole (79.9 [16.2]) and initial levodopa (82.5 [14.6]) groups (P=.19). Dopaminergic motor complications (wearing off, on-off effects, or dyskinesias) were more common in the initial levodopa group (68.4%) than in the initial pramipexole group (50.0%) (P=.002), although disabling dyskinesias were uncommon in both groups. The mean (SD) Epworth Sleepiness Scale score was significantly higher in the initial pramipexole group (11.3 [5.8]) than in the initial levodopa group (8.6 [4.7]) (P_.001). Mean (SD) changes from baseline in the total Unified Parkinson's Disease Rating Scale score did not significantly differ between the initial pramipexole (2.4 [17.4]) and initial levodopa (0.5 [17.1]) groups (P=.11).

The policies of initial pramipexole and initial levodopa use followed by open-label levodopa use resulted in similar self-reported disability 6 years after randomization. Persistent differences favoring initial pramipexole were seen in the rates of dopaminergic motor complications, with less severe somnolence favoring initial levodopa.[7]

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Antidepressant Effects of MIRAPEX

Several studies have examined the effects of pramipexole on depression and depressive disorders in both Parkinson's disease (PD) patients and patients without PD. Summaries of such studies appear below with the most recent described last.

A study by Londborg et al.[1] with a double-blind, placebo-controlled, parallel group design randomized patients to one of three fixed doses of pramipexole (1 mg, 3 mg or 7 mg daily or placebo). The efficacy, tolerability and dosage of pramipexole in treating major depression was studied in 32 adult American outpatients (18F,14M) with a mean age of 38 years and meeting DSMIII-R criteria for major depression.[1] There were no significant differences in the demographic variables, nor were there any significant differences seen in depression severity at baseline. There were nine patients in the placebo group, eight in each of the 1 mg and 3 mg groups, and seven in the 7 mg group. The HAM-D_{17} score had to be at least 22 and the depressed mood was rated at least three on item #1. The length of the study treatment was eight weeks, with a post-study taper of two weeks. Pramipexole 0.25 mg daily was titrated to the fixed dose level over two weeks. A dose reduction of 0.5 mg was allowed for intolerance in patients in the 1 mg group, and a reduction of 1 mg was allowed in the 3 mg and 7 mg groups. Efficacy was measured by mean change in the HAM-D_{17} from baseline by the CGI-I of at least "much improved," as well as by change in the Core Depression Cluster (HAM-D_{17} items 1, 2, 3 and 7). Adverse events were recorded at each visit. Of the 32 patients in the study, 62% (20/32) completed eight treatment weeks. Mean HAM-D_{17} scores ranged from 23.1 to 25.1 and CGI severity from 4.75 to 5.25 at baseline. Repeated-measures for the HAM-D_{17} were significant for treatment groups ($p<0.039$) and approached significance for interaction between treatment and visit ($p<0.057$). Pramipexole was significantly superior to placebo for the proportion of patients at least much improved at endpoint ($p<0.013$). The Core Depression Cluster (low mood, loss of interest) was significantly more improved for the pramipexole treated patients as assessed by repeated ANOVA (main effect of group, $p<0.028$; treatment by visit interaction, $p<0.007$). The greatest improvement occurred with the 3 mg dose (the HAM-D_{17} mean scores, CGI Improvement, and Core Symptoms-HAM-D_{17} items 1, 2, 3, and 7.) No serious adverse events were recorded, but 11/23 (48%) of patients were intolerant of pramipexole with increased dosing so that 5/7 (71%) were intolerant of the 7 mg group. Adverse events reported were nausea, headache, vomiting, sedation and dizziness. Nearly all patients (10/11) on active drug who discontinued treatment did so due to dose-related nausea. The investigators concluded that pramipexole was effective in the treatment of major depression of marked severity, but its utility may be limited by nausea. Further study is warranted, particularly in 2 mg and 3 mg doses.[1]

Sporn, et al[2] studied the use of pramipexole as an adjunctive medication in refractory bipolar and unipolar depression in a naturalistic setting.[2] Data was retrospectively reviewed from psychiatrists whose patients had an inadequate response to at least one full antidepressant trial who had received open-label, adjunctive pramipexole. Thirty-two DSM-IV patients (15M, 17F) were diagnosed with unipolar and bipolar patients (20 and 12 respectively) with a mean age of 41.5±11.4 years. Ratings at each visit to the clinic, utilizing the CGI-I and Global Assessment of Functioning scales (GAF) were performed. Treatment response was defined as both CGI-I score ≤ 2 and a reduction in CGI-score ≥ 1 compared to baseline (prior to pramipexole augmentation). Pramipexole in a mean dose of 0.70 mg daily, mean duration of 24.4 weeks was effective in 6/12 (50%) of bipolar depressed patients and in 8/20 (40%) of unipolar depressed patients, mean duration of follow-up of 24.4 weeks. There was one case of transient hypomania. Eight patients discontinued pramipexole due to lack of response and four due to side effects. Side effects noted in this study included tremor (n=4), sedation (n=4), irritability (n=2), dry mouth (n=2); nausea, tics, urinary hesitancy, diminished appetite, vivid dreams, insomnia, transient word-finding difficulty, dizziness (all n=1). There was a significant increase ($P<0.0001$) in GAF score. The authors concluded that pramipexole maybe a useful, well-tolerated,

adjunctive treatment for unipolar and bipolar depression. These retrospective uncontrolled, naturalistic pilot data need confirmation by controlled trials.[2]

In another study by Szegedi, et al. under open-label and nonrandomized conditions without placebo or active control group, the safety and tolerability of the antidepressant properties of pramipexole was explored in 26 male and female hospitalized patients (age range, 18 to 70 years) for major depression.[3] Pramipexole total daily doses ranged from 1.75 to 9.0 mg, utilizing a 14-day dose escalation phase to reach the highest attainable dose or target dose. This dose was then administered unchanged for an additional two weeks in this 28-day treatment period. The study was terminated at the 6.25 mg dose level due to the dose-limiting appearance of nausea, restlessness, headache and insomnia. The most common side effects were: nausea (50%, N=13), agitation (42%, N=11), headache (38%, N=10), insomnia (31%, N=8), as well as constipation, vomiting, fatigue and pain in the stomach or limbs (15% each, N=4 each). Treatment-emergent adverse events occurred in 15% or more of the 26 patients. A total of eight patients (30.8%) reported 13 individual severe adverse events (whether or not related to pramipexole). These included agitation and insomnia (2 events each), tachycardia, pulmonary embolism, pneumonia, depression, nausea, anxiety, postural hypotension, visual hallucinations (one event each). Five of these severe adverse events (visual hallucinations, insomnia, agitation, anxiety, nausea, orthostatic dysregulation, restlessness and dizziness) occurred in a single patient receiving the highest dosage allowed in the protocol (9 mg daily). The pramipexole dosage was reduced to 6.0 mg daily for four days, and this was followed by a further reduction to 3.0 mg daily for seven days. The symptoms resolved within one week, and the patient received the drug for the planned period of observation. No clinically important vital sign, electrocardiographic or laboratory abnormalities were noted. Five patients dropped out during the dose escalation phase (four due to adverse events and one from lack of efficacy). All 26 patients were included in the safety and efficacy analyses.[3] At the beginning of the study, 25 of the 26 patients (96%) were markedly or severely ill by the CGI severity scale; at the final visit, seven of 26 patients (27%) of patients remained in this category. Pramipexole resulted in consistent reductions in clinical depression, as demonstrated by the Montgomery-Asberg Depressive Rating Scale (MADRS), Bech-Rafaelsen Melancholia Scale (BRMES) and HAM-D_{17}. According to the CGI scale, pramipexole gave substantial benefit in most patients with much improvement or very much improvement in 13 patients (50%). The effect was rated as marked or moderate improvement in 18 patients (69%). The results on the CGI were consistent with the changes on the other rating scales. On the MADRS Scale, 12 showed an improvement of ≥35% compared with the baseline score, whereas the respective number of patients was 10 for BRMES and 13 for the HAMD-17. Pramipexole was maintained for >28 days in five patients (up to 524 days of treatment); two of the five demonstrated further decreases in depression scores, and three demonstrated minor increases. Long-term pramipexole was generally well tolerated until electively terminated so as to try other therapies. Results demonstrated sufficient antidepressant properties and safety in severely depressed patients to justify a larger double-blind, placebo-controlled trial.[2] Results also supported the safety and tolerability of rapid pramipexole escalation for the treatment of major depression and dosages up to 6.25 mg daily.[3]

In a study by Corrigan, et al., pramipexole was studied in 174 patients with major depression, with or without melancholia and without psychotic features.[4] Three daily dose levels (0.375 mg, 1.0 mg, and 5.0 mg) were compared to fluoxetine 20 mg and placebo in a randomized, double-blind, parallel-group study. Following a 1 week placebo run-in period, patients were treated for 8 weeks, had a post-study follow-up (week 9), and were evaluated primarily with the HAM-D_{17}, MADRS, and Clinician's Global Impressions-Severity of Illness scale (CGI-SI). All patients who received one dose of study medication were included in the observed-case analysis (ie. no missing data were replaced). Results indicated that by endpoint (week 8), patients receiving pramipexole at the 1.0 mg daily dose had significant improvement over baseline compared to the placebo group by measure of the HAM-D_{17}, MADRS, and CGI-SI. Significant improvement in this dose group was also observed at other time points. The most obvious improvement was seen in the pramipexole 5.0 mg group, although a substantial dropout rate for this group precluded statistical tests vs. placebo late in the study. Patients taking fluoxetine also showed significant improvements at endpoints on the MADRS and earlier in the study on the HAM-D. No new or unusual safety concerns were generated during the study. Pramipexole helped safely alleviate the symptoms of depression at 1.0 mg per day and particularly in those patients who could tolerate all escalation to 5 mg daily.[4]

Dell'Osso et al. reported on twenty patients hospitalized for major depressive episode that were unresponsive to at least one tricyclic antidepressant and/or selective serotonin reuptake inhibitor received pramipexole (0.375 mg/day) in addition to their current antidepressant treatment.[5] The dose of pramipexole was increased 0.375 mg weekly. Seven patients were diagnosed with unipolar disorder, 13 with bipolar disorder, 7 with comorbidity of panic disorder, 6 with obsessive-compulsive disorder, and 1 with social phobia. At baseline the mean MADRS score was 35.6 and the mean CGI severity score was 4.8. Ten of 16 patients were considered responders at 4 weeks: 8 out of 10 were considered responders at 8 weeks.[6] Two patients discontinued treatment due to dysphoria and hypotension. Larger studies with longer follow-up are needed to confirm these results and to examine whether adjunct pramipexole therapy prevents recurrences.[5]

Conte, et al. studied six patients with bipolar depression received pramipexole beginning at 0.25 mg three times daily.[6] The dose was increased by 0.25 mg, 3 times daily every 35 days until a response was achieved or until side effects prevented further increases.[6] Patients received long-term treatment with at least one mood stabilizer. All had been previously hospitalized for both manic and depressive episodes and were prone to antidepressant-induced switching into mania. Normothymia was achieved by all subjects, but 2 subsequently developed manic symptoms and another was withdrawn from the study prior to becoming fully manic. One became psychotic. Only 1 patient reached normothymia and remained stable during and after pramipexole treatment. Improvement of depressive symptoms, but not switching into mania, was correlated with the pramipexole dose. Pramipexole was not effective at doses <0.5 mg, 3 times daily. Switching into mania appears to be only somewhat less frequent with pramipexole than with standard antidepressants, and it is not prevented by the addition of mood stabilizers.[6]

The effects of pramipexole (PPX) and ropinirole (RPN) were studied via a chart review by Perugi et al. of 18 patients (7 M, 11 F, mean age 55 years old, range 30-75 years) with a DSM-III-R bipolar NOS (Bipolar II) major depressive episode. Dopamine agonists (DA) were added to ongoing treatments with other antidepressants and mood stabilizers (lithium, fluvoxamine, imipramine, nortriptyline, citalopram, despiramine, venlafaxine, valproate, carbamazepine, gabapentin, lamotrigine, trazodone and trimipramine) to which patients had not responded after at least 8 weeks.[7] Clinical state and adverse effects had been assessed at each visit. Ten patients and 8 patients received RPN in doses of 0.375 mg/day and 0.75 mg/day respectively. Treatment lasted a mean of 17.6 weeks (range of 4 to 34 weeks) with a dose range of 0.75 to 1.5 mg/day for PPX and 1.5 to 5 mg/day for RPN depending on clinical response. Mean final doses were 1.23 mg/day for PPX and 2.97 mg/day for RPN. Final improvement in CGI scores of 1 or 2 were considered to be responders. The mean change according to the CGI severity scale was statistically significant ($p<0.0002$). Of the 18 patients, 8 were considered responders (4 with each drug). Of these, 5 patients had a CGI score of 1 (marked improvement) and 3 had a score of 2 (moderate improvement). Ten were considered non-responders; 2 had a score of 4 (no change) and 1 had a score of 5 (deterioration). Five patients manifested a transient response (an initial improvement for 4 weeks, followed by a loss of response at the end of the study). The average time to positive response was 1.7 weeks (range 1-4). Adjunctive agonists were well tolerated by most patients. Only one patient became worse (final CGI=5), and had to stop PPX due to nausea, irritability and increased agitation. The remaining patients showed an improvement in both mood and depression. Adverse effects related to PPX and RPN (nausea, irritability, agitation, headache, insomnia, increased sexual drive and vomiting) did not produce a clinically relevant impairment and usually occurred when doses were increased and tended to diminish with time. Results suggested that both agonists were well tolerated, did not interact with concomitant psychotropic medications, and thus may be of adjunctive benefit in the management of resistant bipolar depression.[7]

In an 8-month, open-label, randomized, multicenter comparative study conducted by Rektorova et al, (Czechoslovakia), the effects of pramipexole and pergolide as add-on to levodopa therapy on depression (MADRS) were studied in 41 non-demented patients (25 M, 16F) with advanced Parkinson's Disease (PD) and mild or moderate depression.[8] Motor symptoms (UPDRS III), motor complications (UPDRS IV), activities of daily living (UPDRS II and VI) and depressive symptoms as measured by a Self–Rating Depression Scale by Zung (Zung SDS) were evaluated by a blinded independent observer. All patients suffered from fluctuations and/or dyskinesias; none of them were on antidepressant medication during the study and for at least four weeks prior to the start of the study. In both groups there was a statistically significant decrease (significance level was 1%) in both UPDRS III and IV between the first and the last visit: there was no significant difference between the groups. In both groups, a

significant decrease in the total levodopa dosage occurred. There was a significant decrease (significance level was 1%) of the total Zung SDS score, with no significant difference between the groups. The decrease of the total MADRS scores reached statistical significance (5%) only in the pramipexole group. When comparing the two groups, the decrease was significantly more pronounced in the pramipexole group. The authors concluded that the antidepressant effect of pramipexole was seen in patients with PD while no conclusions could be made with regard to antidepressant effect of pergolide.[8]

Ostow concluded that pramipexole caused impressive alleviation of depression [9] in a study of 22 patients (11 M, 11 F, range20-60 years of age). Side effects were relatively few and included nausea, sleepiness, and unremitting alertness, which for some patients led to a sleep deficit. Complaints of confusion, sleepiness, and the "feeling wired" and "spacey sensation" were recorded. Results suggested that pramipexole has significant antidepressant potency and is no less effective than any of the other antidepressants in use. Patients received pramipexole 0.5-3 mg daily combined with other antidepressants. Following treatment with pramipexole, 13 of the 22 patients experienced complete or impressive alleviation of their depressive state. Six patients were taking pramipexole alone, and 7 had pramipexole added to their current antidepressant regimen. Pramipexole contributed to alleviation of depressive component of the illness, but that was not enough to resolve the complex clinical picture of these 5 patients. One patient had to stop taking pramipexole at a dose of 3 mg/day due to side effects. Three patients did not tolerate pramipexole. Five patients took no more than 0.5 mg/daily or did well with less. Four did well taking 0.5-1.0 mg/daily. Eight required 1-3 mg/daily and 5 required > 3 mg/daily. Confusion, sleepiness, and the feeling of "being wired" and "spacey sensations" were recorded. There were no instances (cases) in which pramipexole was not helpful.[9]

The antidepressant efficacy and tolerability of adjunctive pramipexole was studied by Lattanzi et al. in 37 patients with drug-resistant major depression (DSM-IV); 16 had unipolar depression and 21 had bipolar depression.[10] Pramipexole was added to antidepressant treatment with tricyclics or selective serotonin reuptake inhibitors at increasing doses from 0.375 to 1.0 mg/daily. Two independent response criteria were utilized: a >50% reduction of the Montgomery-Asberg Depressive Rating Scale (MADRS) total score and a score of 1 or 2 on the Clinical Global Impression scale (CGI-I) at endpoint. Side-effects were assessed by the Dosage Record Treatment Emergent Symptom Scale (DOTES). Six patients dropped out in the first week. Of the 31 patients included in the analyses, 19 completed the 16-week follow-up. The mean maximal dose of pramipexole was 0.95 mg/day. Mean scores on MADRS decreased from 33.3 ± 8.4 at baseline to 13.9 ± 11.5 at endpoint ($p < 0.001$) and the CGI-S decreased from 4.6 ± 0.8 at baseline to 2.8 ± 1.3 at endpoint ($p < 0.001$). At endpoint, 67.7% (21/31) of patients were responders on MADRS and 74.2% on CGI-I. Of the 37 patients enrolled, 10 discontinued pramipexole because of adverse events. Hypomania occurred in 2 and resulted in pramipexole being discontinued; most common side effects among completers were tremor (8 patients) and excitement (psychomotor agitation) (6 patients). The authors concluded that the preliminary data suggested addition of pramipexole to antidepressant treatment may be effective and well tolerated in patients with resistant major depression.[10]

In another study (Reichmann et al. and Lemke et al.), the purpose was to confirm the beneficial effects of pramipexole on the core symptoms of Parkinson's disease (with a focus on tremor), as well as to assess its antidepressant activity, during routine clinical practice.[11,12] The study also aimed to demonstrate the practicability of the Snaith-Hamilton Pleasure Scale (SHAPS-D), the Tremor Impact Scale (TIS) and the Short Parkinson's Evaluation Scale (SPES) under routine clinical practice conditions in a prospective observational design. Data for 657 outpatients with Parkinson's disease were collected from German hospitals and specialist practices. The majority of patients was Hoehn & Yahr stage II or III and was receiving levodopa. Pramipexole was initiated at a dosage of 0.375 mg/day (administered three times daily) and titrated upwards as needed at weekly intervals over a 4-week period to a maximum dosage of 4.5 mg/day (three times daily). Clinical evaluation was performed at baseline, at the end of the titration phase and at the end of the 9-week study period. Patients were assessed by way of the German questionnaire version of the physician-assessed SPES, the self-evaluated TIS and the SHAPS-D. Anhedonia was present in 45.7% of all patients and in 79.7% of the depressed patients with Parkinson's disease. Mild depression was present in 47% and moderate to severe depression in 22% of the patients. At the end of the study period, the mean dose of pramipexole was 1mg per day. Pramipexole significantly reduced anhedonia in patients who had associated depression (SHAPS-D questionnaire). Pramipexole significantly improved SPES subscores for motor symptoms,

psychological status, complications of therapy and activities of daily living. Pramipexole also reduced the detrimental effect of tremor on activities of daily living and social interactions, as assessed by patients via the TIS. Internal consistency of SPES subscales, TIS, and SHAPS-D was unaltered between the initial evaluation and follow-up. Pramipexole was well tolerated and accepted by the vast majority of physicians and patients. The authors concluded that in addition to ameliorating the core symptoms of akinesia and rigidity in Parkinson's disease, pramipexole improves tremor and depressive symptoms in routine clinical practice.[11,12]

Barone P, et al.[13] conducted a 14-week randomized trial to compare pramipexole with an established antidepressant, sertraline, in depressed Parkinson's disease patients without motor complications and on stable levodopa treatment. The study was conducted at 7 centers in Italy and included 67 outpatients suffering from both idiopathic Parkinson's disease and major depression but no history of motor fluctuations or dyskinesia. The subjects received open-label pramipexole (dose of 1.5 to 4.5mg/day) or sertraline (at 50mg/day). The Hamilton Depression Rating Scale (HAM-D) score decreased in both groups throughout the 12 week study period. The proportion of patients who recovered as defined by a final HAM-D score ≤8 was significantly higher in the pramipexole group compared to the sertraline group (60.6% compared to 27.3% (p=0.006). Patient's self ratings (using the Zung Self-Rating Depression Scale) were improved in both groups. Eleven patients reported at least one adverse event. Three of these were in the pramipexole group (9.1%; 4 events: one case each of dyskinesia, nausea, abdominal pain, and hypothyroidism) and eight were in the sertraline group (24.2%; 11 events: 2 cases of vertigo, 2 of nausea, and one each of anxiety, abdominal pain, diarrhea, asthenia, palpitation, influenza, and tremor). All events were rated as mild (5 events in the sertraline group) or moderate (4 in the pramipexole group and 6 in the sertraline group). No patients withdrew from the pramipexole group, but 5 withdrew from the sertraline group for the following reasons: nausea (2 cases), vertigo, anxiety, and abdominal pain. The Unified Parkinson's Disease Rating Scale (UPDRS) Part II motor subscore improved for both groups, but was only statistically significant in the pramipexole group. The implication of this study is that dopamine agonists may be an alternative in treating depression in Parkinson's disease at the same doses used to manage motor symptoms.[13]

A meta-analysis by Leentjens AF, et al.[14] evaluated the effect of pramipexole on mood and motivational symptoms in patients with PD. Seven of the 14 pramipexole trials in the manufacturer's database that were randomized, double-blind, placebo controlled, included part I of the Unified Parkinson's Disease Rating Scale (UPDRS) as a secondary outcome measure; the primary outcome for all trials was the severity of motor symptoms of PD. These 7 trials (N=1296) formed the basis of this meta-analysis. Only patients with baseline scores >0 on item 3 (mood) and item 4 (motivation) were included with separate analyses conducted for each. The outcome of interest was improvement of scores. No improvement was defined as unchanged scores or increased scores (range, 0-4). Odds ratios (ORs), 95% CIs, and Cochrane-Mantel-Haenszel tests were used to compare rates of improvement and no improvement and stratified by trial. Six of the 7 studies appeared in peer- reviewed journals and although the published studies were usually limited to reporting on motor symptom results, the authors had access to data not reported in the original manuscripts. In the pooled data set, 480 patients had a baseline score >0 on item 3 (mood), 59.8% were male, and the mean age was 63.3 years. Of the pramipexole treated patients, 64.7% showed improved mood symptoms compared to 43.4% of placebo treated patients (OR weighted by trial = 2.41; P<0.001). In the pooled data set, 570 patients had a baseline score >0 on item 4 (motivation), 64.9% were male, and the mean age was 64.1 years. Motivational symptoms improved in 63.2% of pramipexole treated patients compared to 45% of placebo treated patients (OR weighted by trial = 2.06; P<0.001). This meta-analysis suggests that pramipexole improves mood and motivational symptoms in PD patients who do not have a major depressive disorder. Further investigation is needed to assess its clinical value in treating depressive and apathetic syndromes.[14]

Barone P, et al. conducted a 12-week randomized double-blind study[15] to prospectively assess the efficacy of pramipexole versus placebo in depression associated with Parkinson's disease. In 76 international centers, 296 patients received either pramipexole or placebo. All patients had a modified Hoehn-Yahr stage I-III with stable motor function for at least the prior 4 weeks. Patients also had to have stable treatment for their PD without dopamine agonists for at least the prior 4 weeks. All patients had to have depressive symptoms as documented with a baseline score on the Geriatric Depression Scale (5 item GDS) of ≥ 5 and a score ≥ 2 on the UPDRS Part I question #3. Flexible dose administration was allowed during the first 5 weeks to optimize the pramipexole dose to between 0.125

to 1.0 mg three times a day. Other antidepressants were allowed as long as the dose had been stable and unchanged for at least the prior 6 week period. The primary endpoint was a change from baseline for the Beck Depression Inventory (BDI-IA) score. A change in the GDS score was also monitored. One hundred and thirty-nine (96.5%) of the initial 144 patients in the pramipexole group provided BDI and GDS data, compared to 148 (97.4%) of the initial 152 patients in the placebo group. Baseline mean BDI and GDS scores were similar for both groups. At the end of 12 weeks, the mean BDI score (adjusted for baseline and country) had improved by 5.9 (0.5) versus 4.0(0.5) for pramipexole versus placebo to 13.1 (0.5) versus 15.0(0.5) (P=0.010 ANCOVA). Similarly, the mean GDS score also improved by 2.5(0.3) versus 1.7(0.3) to 6.3(0.3) versus 7.1(0.3) (P=0.035) in the pramipexole versus placebo groups. In this study, pramipexole improved depressive symptoms associated with PD significantly more than placebo.[15]

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