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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* JONATHAN BROTCHE and MICHAEL HILL

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Appeal 2015-004321  
Application 13/077,478  
Technology Center 1600

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Before MELANIE L. McCOLLUM, JEFFREY N. FREDMAN, and  
DAVID COTTA, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal<sup>1</sup> under 35 U.S.C. § 134 involving a method of extending the duration of on-time in a patient undergoing dopamine replacement therapy for Parkinson’s Disease. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

*Statement of the Case*

*Background*

“Parkinsonism is one of the most prevalent movement disorders and comprises a syndrome of symptoms characterised by slowness of movement (bradykinesia), rigidity and / or tremor” (Spec. 1). “Motor fluctuations can

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<sup>1</sup> Appellants identify the Real Party in Interest as Motac Neuroscience Limited (*see* App. Br. 1).

manifest as a ‘wearing-off’ of anti-parkinsonian efficacy, where a good anti-parkinsonian effect of the dopamine-replacement therapy does not last as long as initially observed, and ‘on-off syndrome’ where the patient experiences disabling fluctuations in mobility (i.e. switching between parkinsonian and treated in an unpredictable manner)” (Spec. 2).

*The Claims*

Claims 1, 2, 6, 7, and 14–19 are on appeal.<sup>2</sup> Claim 1 is representative and reads as follows:

1. A method of extending the duration of on-time in a human patient undergoing dopamine replacement therapy for Parkinson’s Disease, said method comprising at least once daily oral administration of a therapeutically effective dose of at least 0.01 µg/kg body weight of a selective 5-hydroxytryptamine 1a receptor agonist to the human patient having Parkinson’s Disease and undergoing dopamine replacement therapy for the treatment of Parkinson’s Disease, wherein the patient exhibits wearing-off of anti-parkinsonian efficacy of the dopamine replacement therapy or has developed “on-off” syndrome, and wherein the at least once daily oral administration of a therapeutically effective dose of at least 0.01 µg/kg body weight of a selective 5-hydroxytryptamine 1a receptor agonist increases the duration of on-time in the human patient.

*The Issues*

A. The Examiner rejected claims 1, 2, 6, and 16–19<sup>3</sup> under 35 U.S.C. § 103(a) as obvious over McLean,<sup>4</sup> Galvan,<sup>5</sup> Nomoto,<sup>6</sup> Liu,<sup>7</sup> Zhuang,<sup>8</sup> and Bonifati<sup>9</sup> (Ans. 2–8).

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<sup>2</sup> Claims 8–13 were withdrawn in the Response to Election/Restriction filed Dec. 14, 2011.

B. The Examiner rejected claim 7 under 35 U.S.C. § 103(a) as obvious over McLean, Galvan, Nomoto, Liu, Zhuang, Bonifati, and Paul<sup>10</sup> (Ans. 8–9).

C. The Examiner rejected claims 14 and 15 under 35 U.S.C. § 103(a) as obvious over McLean, Galvan, Nomoto, Liu, Zhuang, Bonifati, and Rinne<sup>11</sup> (Ans. 9–11).<sup>12</sup>

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<sup>3</sup> The Examiner inadvertently omitted claim 16 from the statement of rejection, but referred to claim 16 in the body of the rejection, rendering the error harmless (*see* Ans. 2).

<sup>4</sup> McLean et al., US 6,300,329 B1, issued Oct. 9, 2001 (“McLean”).

<sup>5</sup> Galvan, M., WO 93/13766 A1, published July 22, 1993 (“Galvan”).

<sup>6</sup> Nomoto et al., *Effects of 5-HT<sub>1A</sub> Serotonin Receptor Agonists on Parkinsonism*, 79 JAPANESE J. PHARMACOLOGY 43 (1999) (“Nomoto”).

<sup>7</sup> Liu et al., *A Comparative Study on Neurochemistry of Cerebrospinal Fluid in Advanced Parkinson’s Disease*, 6 NEUROBIOLOGY DISEASE 35–42 (1999) (“Liu”).

<sup>8</sup> Zhuang et al., *Synthesis of (R,S)-trans-8-Hydroxy-2-[N-n-propyl-N-(3’-iodo-2’-propenyl)amino]tetralin (trans-8-0H-PIPAT): A New 5-HT<sub>1A</sub> Receptor Ligand*, 36 J. MEDICINAL CHEM. 3161–3165 (1993) (“Zhuang”).

<sup>9</sup> Bonifati et al., *Buspirone in Levodopa-Induced Dyskinesias*, 17 CLINICAL NEUROPHARMACOLOGY 73–82 (1994) (“Bonifati”).

<sup>10</sup> Paul et al., *D1-like and D2-like Dopamine Receptors Synergistically Activate Rotation and c-fos Expression in the Dopamine-depleted Striatum in a Rat Model of Parkinson’s Disease*, 12 J. NEUROSCIENCE 3729–3742 (1992) (“Paul”).

<sup>11</sup> Rinne et al., *Entacapone Enhances the Response to Levodopa in Parkinsonian Patients with Motor Fluctuations*, 51 NEUROLOGY 1309–1314 (1998) (“Rinne”).

<sup>12</sup> The Examiner also rejected claims 1, 2, 6, 7 and 14–19 under 35 U.S.C. § 112 (a) as failing to comply with the enablement requirement. Ans. 11. In the Examiner’s Answer, the Examiner withdrew this rejection. *Id.* This issue is thus not a part of this appeal.

Because the same issues are dispositive for all of the rejections, we will consider these rejections together. Also, we limit our consideration of the merits of the appealed rejection to the elected species. *See Ex parte Ohsaka*, 2 USPQ2d 1460, 1461 (BPAI 1987). Thus, we read the claims as limited to the use of the elected 8-OH-PIPAT compound as the active 5HT1a receptor agonist in combination with parkinsonism as the elected movement disorder and do not address the broader scope of the claims (*see* Response to Election/Restriction filed on Dec. 14, 2011).

The Examiner finds McLean teaches “a method of treating Parkinson’s disease comprising administering a dopamine D2 receptor agonist in combination with a 5HT 1a receptor agonizing agent in amounts to treat Parkinson’s disease” (Ans. 2). The Examiner acknowledges that McLean “does not teach a method of extending the duration of on-time” or 8-OH-PIPAT as an agonist (Ans. 3).

The Examiner finds that Galvan teaches “5HT 1a receptor agonists of formula (I) treat involuntary movements in parkinsonism”; that Nomoto teaches “5-HT 1a serotonin receptor agonist tandospirone improved the walking in patients with advanced stages of Parkinson’s disease”; and that Zhuang teaches 8-(OH)-PIPAT is a potent 5HT 1a agonist (Ans. 3–5).

The Examiner finds that Liu teaches that “both PD-A and PD-B patient who were under levodopa treatment showed comparative amounts of the serotonin 5-HT concentrations . . . in which both have decreased 5-HT activity” (Ans. 4). The Examiner further finds that Bonifati teaches “5HT-1A agonist buspirone improve the symptoms of levodopa-induced

dyskinesia without worsening the extrapyramidal symptoms in Parkinson's Disease patients" and "[b]usprione was able to increase on-time and decrease off time compared to the basal visit, and slightly decrease the extrapyramidal symptoms in on time compared to the placebo" (Ans. 5).

The Examiner finds it obvious

that combining two compounds that treat parkinsonism will potentially increase the time the patient is not experiencing movement disorders (on-time). Particularly, since each drug treats parkinsonism at different receptors, one would reasonably expect that the "on-time" would be extended because when one drug becomes ineffective the other drug is able to treat parkinsonism from a different receptor.

(Ans. 6).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the prior art renders it obvious to extend "on-time" duration by treatment of a patient with parkinsonism undergoing dopamine replacement therapy by further treatment with 8-OH-PIPAT and in cases where "the patient exhibits wearing-off of anti-parkinsonian efficacy of the dopamine replacement therapy or has developed 'on-off' syndrome" as required by claim 1?

*Findings of Fact*

1. McLean teaches

a method for treating Parkinson's Disease in a mammal, including a human, comprising administering to a mammal in need of such treatment a D2 receptor agonizing agent in combination with a 5HT<sub>1A</sub> receptor agonizing agent, wherein the two foregoing active agents are present in amounts such that the combination of such agents is effective in treating Parkinson's Disease.

(McLean 3:23–30).

2. McLean teaches “[e]xamples of 5HT<sub>1A</sub> receptor agonizing agents that can be used in the methods of this invention include . . . buspirone” (McLean 4:51–54).

3. McLean teaches the “5HT<sub>1A</sub> receptor agonist will be administered in an amount ranging from about 5-90 mg per day, in single or divided doses” (McLean 9:25–27).

4. Galvan teaches “the use of 5HT<sub>1A</sub> receptor agonists . . . to treat involuntary movements in . . . parkinsonism” (Galvan, abstract).

5. Nomoto teaches “stimulation of 5-HT<sub>1A</sub> receptor agonists . . . increased spontaneous locomotor activity in MPTP-treated animals and reversed akinesia in patients on advanced stages of the disease” (Nomoto, abstract).

6. Liu teaches that “compared to PD-A, PD-B tends to have a severely decreased 5-HT activity” and “that PD-B has a lower serotonergic activity than PD-A. This may explain the emotional and cognitive deficits that are commonly seen in PD-B” (Liu 37, col. 2 to 38, col. 1).

7. Liu teaches “symptoms that often accompany PD-B such as depression, loss of appetite and weight, sleep disturbances, persistent occurrence of nausea and vomiting, somnolence, yawning, vivid dreams, myoclonus, and hallucinosis are all related to serotonergic dysfunctioning” (Liu 38, col. 2).

8. Liu teaches “[t]reatment of such symptoms is the addition of one of the selective serotonin reuptake inhibitors (SSRI) . . . our observation has shown the hypokinetic symptoms of akinesia and bradykinesia,

manifested as gait disorders, including gait freezing, postural instability, and masked faces experience significant alleviation following the administration SSRIs (Liu 38, col. 2 to 39, col. 1).

9. Zhuang teaches that 8-OH-PIPAT is more sensitive than other 5HT<sub>1A</sub> agonists and “offers several unique advantages, including high specific activity, high binding affinity, and low nonspecific binding, all of which make it an excellent probe for the investigation and characterization of 5-HT<sub>1A</sub> receptors” (Zhuang, abstract).

10. Bonifati teaches “buspirone treatment was associated with a significant reduction in the severity of involuntary movements (Fig. 4). In particular, buspirone had marked effects on dyskinesias in the five patients with more severe LID [levodopa-induced dyskinesias]. In two cases of intermediate severity, LID totally disappeared during the L-Dopa test using buspirone treatment” (Bonifati 75).

### *Principles of Law*

A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art . . . it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.

*KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

### *Analysis*

Appellant contends

McLean fails to disclose, either alone or in combination with Galvan, Nomoto, Liu, Zhuang, and/or Bonifati, any method of extending the duration of on-time in a human patient undergoing dopamine replacement therapy for Parkinson’s

Disease . . . wherein the patient exhibits wearing-off of anti-parkinsonian efficacy of the dopamine replacement therapy or has developed “on-off” syndrome

(App. Br. 7).

The Examiner acknowledges that “none of the cited prior art specifically teaches ‘extending the duration of on-time in a human patient undergoing dopamine replacement therapy’” but finds that “Liu et al. and Bonifati et al. provide motivation to treat the levodopa induced effects of on-off time and other levodopa induced side effects with a 5HT<sub>1a</sub> receptor agonist” (Ans. 12 and 14). The Examiner further finds it obvious

to extend the duration of on-time because both dopamine replacement therapy and 5-HT<sub>1a</sub> serotonin receptor agonist are known to treat Parkinson’s disease . . . since each drug treats parkinsonism at different receptors, one would reasonably expect that the “on-time” would be extended because when one drug becomes ineffective the other drug is able to treat parkinsonism from a different receptor.

(Ans. 14).

We find Appellants have the better position. The Examiner has not established that the ordinary artisan would have expected the combination of a 5HT<sub>1a</sub> agonist and dopamine replacement therapy to extend the duration of “on-time” in the particular subpopulation of patients with Parkinson’s disease who experience either “wearing-off” or “on-off” syndrome. We recognize that McLean, Liu, and Bonifati suggest treating Parkinson’s disease patients in general with both compounds (FF 1, 8, 10). However, none of the cited art suggests treating the subpopulation of Parkinson’s patients who experience either “wearing-off” or “on-off” syndrome. The

Blackburn Declaration<sup>13</sup> further supports this position by noting “Liu et al does not demonstrate or suggest, that there is any correlation between motor fluctuations characterized by wearing-off of the efficacy of dopamine replacement therapy or as on-off syndrome and decreased 5-HT activity” (Blackburn Dec. ¶ 10).

In addition, the Examiner has not established that “wearing-off” or “on-off” syndromes are necessary consequences of dopamine treatment, or that “wearing-off” syndrome would necessarily be treated by continued administration of combination of a 5HT<sub>1a</sub> agonist and dopamine replacement therapy. Therefore, the evidence of record does not demonstrate that treatment of Parkinson’s disease generally will necessarily result in the treatment of either specific “wearing-off” or “on-off” syndrome. In *Perricone*, the Federal Circuit distinguished between the topical application of a lotion to skin generally to prevent sunburn, and the topical application of a lotion to treat sunburned skin, finding that the “issue is not . . . whether [the prior art] lotion if applied to skin sunburn would inherently treat that damage, but whether Pereira discloses the application of its composition to skin sunburn. It does not.” *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005). The same analysis applies here. There are clear and express teachings to treat Parkinson’s disease patients with the combination of dopamine replacement therapy and 5HT<sub>1a</sub> agonists, including with 8-OH-PIPAT and in the claimed dosages (FF 1–10).

If those same Parkinson’s disease patients also happened to be have either “wearing-off” or “on-off” syndrome, the treatment might also

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<sup>13</sup> Declaration of Dr. Thomas P. Blackburn, dated May 21, 2009.

necessarily result in extending the duration of “on-time” in patients undergoing dopamine replacement therapy, analogous to the skin treatment at issue in *Perricone*. However, the Examiner has not identified any teaching or suggestion in the prior art to identify and treat “wearing-off” or “on-off” syndromes with the 5HT<sub>1a</sub> agonist. In the same manner that not everyone who applies lotion to their skin will necessarily have sunburn, the evidence of record does not demonstrate that all Parkinson’s disease patients will necessarily have either “wearing-off” or “on-off” syndrome. *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981) (“Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.”).

*Conclusion of Law*

The evidence of record does not support the Examiner’s conclusion that the prior art renders it obvious to extend “on-time” duration by treatment of a patient with parkinsonism undergoing dopamine replacement therapy by further treatment with 8-OH-PIPAT and “wherein the patient exhibits wearing-off of anti-parkinsonian efficacy of the dopamine replacement therapy or has developed ‘on-off’ syndrome” as required by claim 1.

SUMMARY

In summary, we reverse the rejection of claims 1, 2, 6, and 17–19 under 35 U.S.C. § 103(a) as obvious over McLean, Galvan, Nomoto, Liu, Zhuang, and Bonifati.

Appeal 2015-004321  
Application 13/077,478

We reverse the rejection of claim 7 under 35 U.S.C. § 103(a) as obvious over McLean, Galvan, Nomoto, Liu, Zhuang, Bonifati, and Paul.

We reverse the rejection of claims 14 and 15 under 35 U.S.C. § 103(a) as obvious over McLean, Galvan, Nomoto, Liu, Zhuang, Bonifati, and Rinne.

REVERSED