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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte BERNARD HUBLOT, RENE LEVY, and
MARIE-EMMANUELLE Le GUERN

Appeal 2014-002580
Application 12/634,249
Technology Center 1600

Before DONALD E. ADAMS, DEMETRA J. MILLS, and
RICHARD J. SMITH, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

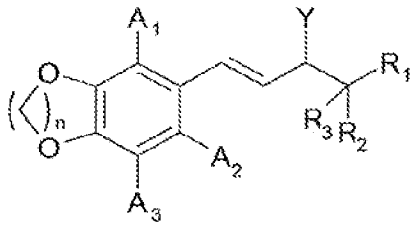
STATEMENT OF CASE

According to the Specification, "[t]he present invention arises from the unexpected observation that resolution of autism symptoms occurs in patients after initiation of treatment with stiripentol." Spec. 2. According to the Specification, it was well known in the art in 2006 that

> the GABAergic system represents an important candidate pathway in autism. The concept is that autism results from an imbalance between inhibitory GABAergic and excitatory glutamatergic pathways. According to this approach, there is overstimulation of the brain with an "inability to filter out excess stimuli from environmental and intrinsic sources" (Collins AL et al, Neurogenetics, 7:167, 2006).

The following claim is representative.

1. A method for the treatment of autism spectrum disorders (ASD) in an individual, comprising administering the individual a prophylactically or therapeutically active amount of at least one compound of the following formula (I):



(I)

in which:

- n represents 1 or 2,
- A_1, A_2 and A_3, identical or different, represent a hydrogen atom, a halogen atom, or a linear or branched alkyl group having from 1 to 4 carbon atoms,
- R_1, R_2 and R_3, identical or different represent a hydrogen atom or a linear or branched alkyl group having from 1 to 4 carbon atoms, and
- Y represents -OH, =0 or -SH;

or a pharmaceutically acceptable salt thereof.

Cited References

Levy	US 5,095,033	Mar. 10, 1992
Chez	US 7,456,224 B2	Nov. 25, 2008
Mei	WO 2008/148023 A2	Dec. 4, 2008

Fisher, Janet L., "The anti-convulsant stiripentol acts directly on the $GABA_A$ receptor as a positive allosteric modulator," *Neuropharmacology* 56; 190-197 (2009).

Grounds of Rejection

Claims 1-11 rejected under 35 U.S.C. § 103(a) as being unpatentable over Fisher in view of Mei, Levy, and Chez.

FINDINGS OF FACT

The Examiner's findings of fact are set forth in the Answer at pages 3-9. The following facts are highlighted.

1. According to the Specification, it was well known in the art in 2006 that

   > the GABAergic system represents an important candidate pathway in autism. The concept is that autism results from an imbalance between inhibitory GABAergic and excitatory glutamatergic pathways. According to this approach, there is **overstimulation of the brain** with an "*inability to filter out excess stimuli from environmental and intrinsic sources*" (Collins AL et al, Neurogenetics, 7:167, 2006).

Spec. 2; emphasis in bold added.

2. Fisher teaches that the $GABA_A$ receptor is a ligand-gated chloride channel and is responsible for most of the fast inhibitory neurotransmission in the mammalian brain and is the target of many drugs in the mammalian brain. Stiripentol (STP) is taught to be a direct positive modulator of the GABA receptors and increases inhibitory GABAergic neurotransmission … . STP is taught to be an anti-epileptic drug used to treat seizure disorders…

Ans. 5.

3. Fisher discloses that stiripentol acts as a weak partial agonist at $GABA_A$ receptors, increasing the sensitivity of the receptor to GABA and providing increased inhibitory GABAergic transmission.[1] P. 194, col 2, sec. 3.5. See also Fig. 6; Abstract.
4. Fisher discloses that stiripentol increases sensitivity of a receptor to GABA. P. 194, Fig 6. Stiripentol increases the response to GABA in a concentration-dependent manner. P. 192; Fig. 2.
5. Fisher discloses that stiripentol can directly activate the $GABA_A$ receptor and act as an agonist at high concentrations. P. 194, col. 2.
6. Mei discloses a composition containing an effective amount of an ErbB4 ligand or agonist to enhance or promote GABA release, i.e., increase GABAergic transmission. By increasing GABA release a sedative effect can be induced in the subject. Abstract; p. 2; Ans. 5.
7. Mei discloses that the

   > ErbB4 agonist ligand induces or promotes ErbB4 activity and thereby induces or promotes GABAergic transmission which increases local concentrations of GABA. Because GABA is an inhibitory neurotransmitter, increased concentrations of GABA induce or promote a sedative effect in a subject. Mei, p. 2.
8. Mei provides compositions and methods for treating one or more symptoms of epilepsy, depression and anxiety, insomnia, stroke, pain, bipolar, **autism** by administering an effective amount of a ErbB4 ligand, for example NRG 1 or a variant thereof. Ligand agonists of ErB4 such as NRG 1 induce a sedative effect in a subject by potentiating GABAergic transmission. Mei, p. 6, ll. 25-30.
9. Mei discloses that

   > the date provided herein is the first to disclose or suggest

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[1] Increased GABAergic activity promotes a sedative effect in a subject. See Mei, FF2. Increased response to GABA results in an increased sedative affect as GABA is an inhibitory neurotransmitter.

> the treatment of neurological disorders such as epilepsy, depression and anxiety, insomnia, stroke, pain, bipolar, **autism** by modulating the NRGI/ErbB4 signal transduction pathway.

Mei, p. 9. The compounds induce a sedative effect by potentiating GABAergic transmission (page 17, lines 9-12). Ans. 8.

10. Mei teaches treatment of neurological disorders including autism by modulation of GABA release (page 1, lines 5-8 and page 2, lines 14-15). Ans. 5.
11. Levy et al. teaches that STP can be administered by the oral route (Col. 2, lines 13-15) and in unit dose form of 100-500 mg, which overlaps with that of claim 6 (Col. 2, lines 26-28). Oral compositions suitable for administration include tablets, capsules (Col. 2, lines 21-23). Ans. 5.
12. Levy discloses that compounds which induce sedation have been known to treat autism symptoms and behaviors. Col. 5, ll. 25-55.
13. Chez teaches that risperidone has been approved by the FDA for the treatment of autism (Col. 3, lines 43-54). Ans. 5.

PRINCIPLES OF LAW

In making our determination, we apply the preponderance of the evidence standard. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office).

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a *prima facie* case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993) (citations omitted).

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

Obviousness

We agree with the Examiner's fact finding, statement of the rejection and responses to Appellants' arguments as set forth in the Answer. We find that the Examiner has provided evidence to support a prima facie case of obviousness. We provide the following additional comment to the Examiner's argument set forth in the Final Rejection and Answer.

With respect to claim interpretation, claim 1 does not require an increase or decrease in GABA. Claim 1 requires only the administration of a stiripentol compound to treat autism.

The Examiner finds that

> Fisher teaches that the $GABA_A$ receptor is a ligand-gated chloride channel and is responsible for most of the fast inhibitory neurotransmission in the mammalian brain and is the target of many drugs in the mammalian brain. Stiripentol (STP) is taught to be a direct positive modulator of the GABA receptors and increases inhibitory GABAergic neurotransmission. . . . STP is taught to be an anti-epileptic drug used to treat seizure disorders…

Ans. 5.

The Examiner relies on Mei as teaching treatment of neurological disorders including autism by modulation of GABA release (page 1, lines 5-8 and page 2, lines 14-15). Ans. 5. Levy teaches that STP can be administered by the oral route (Col. 2, lines 13-15) and in unit dose form of 100-500 mg, which overlaps with that of claim 6 (Col. 2, lines 26-28). Ans. 5. Oral compositions suitable for administration include tablets, capsules

(Col. 2, lines 21-23). Chez teaches that risperidone has been approved by the FDA for the treatment of autism (Col. 3, lines 43-54). Ans. 5.

The Examiner concludes that

> [I]t would be obvious to a person of ordinary skill in the art at the time of the invention to utilize STP in the treatment of autism due to the teachings of Mei et al., which teaches that autism is modulated by GABA release and Fisher which teaches that STP is a direct positive modulator of the GABA receptor and increases inhibitory GABAergic neurotransmission. One would be motivated to utilize STP for treating autism spectrum disorders because it is known to increase inhibitory GABAergic neurotransmission and autism spectrum disorders such as autism, is [sic] known to be treated by modulation of GABA release. Further, one would be motivated to use the guidance of the unit dosage form taught by Levy et al. because Levy et al. teaches the dosage form in conjunction with treatment of epilepsy, and Mei et al. teach that GABA modulation treats both autism and epilepsy, making it obvious to use the same unit dose forms to treat disorders with similar underlying etiologies.

Ans. 6.

Appellants argue that

> Mei does not establish that [Autism Spectrum Disorder] ASD would be linked to a diminished release of GABA, nor that any compound increasing inhibitory GABAergic neurotransmission would treat ASD. Instead, Mei merely indicates that compositions described therein may be useful for treating autism (see page 17, line 1), although no experimental proofs nor any reasoning justifying this allegation are presented. In contrast, Applicants' established experimentally that stiripentol is useful for treating ASD in accordance with the present claims.
>
> In addition, the compositions disclosed in Mei can either increase or decrease GABAergic transmission (see page 17, lines 2-5). Thus, one reading Mei, would not know whether increasing GABAergic transmission or decreasing GABAergic transmission would treat autism, thus not providing any disclosure or suggestion of the present claims. Ultimately, compounds described by Mei are said

> to both increase or decrease the release of GABA by GABAergic neurons.
>
> In contrast, according to Fisher, stiripentol is a positive allosteric modulator (i.e. an allosteric activator) acting directly upon the $GABA_A$ receptor that increases the sensitivity of the receptor to GABA, without increasing the maximum response to saturating GABA concentrations (see page 195, right column, first paragraph of the Discussion section). Accordingly, the compounds of Mei and stiripentol do not share the same mode of action and would be seen by one of skill in the art as not mediating the same therapeutic effects (i) because stiripentol acts on only one type of GABA receptors ($GABA_A$ receptors) while the compounds of Mei will act on all GABA receptors irrespective of their type, and (ii) because the degree by which GABAergic transmission may be increased respectively by stiripentol and by the compounds of Mei is not known and is likely dissimilar.

Br. 8-9.

We are not persuaded. The Examiner's rationale is essentially: there is a shared mode of action between the compounds Fisher and Mei, the ultimate effect of the administration of stiripentol and the compounds of Mei is modulation of GABA, including modulation to produce an increased sedative effect. Mei discloses that their disclosed compounds treat autism. The pending method claims do not recite that the method requires either an increase or decrease of GABA, only that a compound such as stiripentol (which modulates GABA) is required.

Contrary to Appellants' argument above, Fisher discloses that STP does not act only at the $GABA_A$ receptors. Fisher, quoted above, (see page 195, right column, first paragraph of the Discussion section), goes on to state that STP also directly activates the GABA receptor as a weak partial agonist. The activity of STP showed some dependence upon the subunit composition

of the receptor, with α3 or δ containing receptors showing the greatest response, but **was able to potentiate receptors containing any of the α, β, or γ subtypes** and did not require the presence of a γ subunit. *Id.*, emphasis added.

Furthermore, Mei does not need to establish that ASD would be linked to a diminished release of GABA, nor that any compound increasing inhibitory GABAergic neurotransmission would treat ASD. The claims do not require an increase or decrease of GABA neurotransmission. Mei discloses compounds which modulate GABA release treat autism. The Examiner finds that

> Mei teaches treatment of neurological disorders, including autism, by modulating the NRG1/ErbB4 signal transduction pathway. Representative ErbB4 agonist ligands include NRG1; therefore, it is clear that agonist ligands treat autism (page 9, lines 12-24). The compounds induce a sedative effect by potentiating GABAergic transmission (page 17, lines 9-12).

Ans. 8; Mei, p. 17, ll. 9-23. "Mei provides evidence that NRG1 increased depolarization-evoked GABA release from presynaptic terminals and proves a role of ErbB4 in NRG1 regulation of GABAergic transmission. Mei provides further evidence that activation of ErbB4 is required for NRG1's effect (Examples 3 and 4)." Ans. 9. Thus, both the stiripentol of Fisher and the ligands of Mei induce a sedative effect by potentiating GABAergic transmission. One of ordinary skill in the art knowing at the time of the invention that autism is associated with overstimulation of the brain, or has been previously treated with sedating compounds[2], would have looked to

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[2] *See also,* Chez, cited in rejection, which discloses that sedating compounds have previously been used to treat autism. Col. 3, ll. 25-54.

treatments for autism which induce a sedative effect on the brain as outlined in Mei, by potentiating GABAergic transmission such as the compounds of Fisher and Mei.

Appellants do not provide evidence of unexpected results or evidence which counters or addresses the specific disclosures of Mei regarding the potentiation of GABAergic transmission.

Appellants argue that, "the Examiner does not anywhere address the Dhossche reference" submitted in the Appendix to the Brief. Reply. Br. 3. 37 C.F.R. 4.37(c) (v)(2) states that, "A brief shall not include any new or non-admitted amendment, or any new or non-admitted affidavit, or other evidence." The Dhossche and Hahn references were presented for the first time in prosecution in the Brief, and thus are not admitted for consideration.

CONCLUSION OF LAW

The cited references support the Examiner's obviousness rejection, which is affirmed. All claims fall.

No time period for taking any subsequent action in connection with this appeal maybe extended under 37 C.F.R. § 1.136

AFFIRMED