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CARTER, DELUCA & FARRELL LLP
576 BROAD HOLLOW ROAD
MELVILLE, NY 11747

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte MATTHEW DURING

Appeal 2022-000776
Application 16/829,423
Technology Center 1600

Before JEFFREY N. FREDMAN, ULRIKE W. JENKS, and TAWEN CHANG, *Administrative Patent Judges.*

CHANG, *Administrative Patent Judge.*

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 1–10. *See* Final Act. 1. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE but enter a new ground of rejection.

STATEMENT OF THE CASE

"Narcolepsy is a chronic neurological disorder involving a decreased ability to regulate sleep-wake cycles. The most typical symptoms are

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[1] We use the word Appellant to refer to "applicant" as defined in 37 C.F.R. § 1.42(a). Appellant identifies the real party in interest as Ovid Therapeutics Inc. Appeal Br. 1.

excessive daytime sleepiness, abnormal REM sleep, cataplexy, sleep paralysis, and hallucinations. Other symptoms may include automatic behaviors and night-time wakefulness. Not all symptoms appear in all patients." Spec. ¶ 3. The Specification states that, although there is no cure for narcolepsy, symptoms are treatable with medications, including central nervous system stimulants, antidepressant medications, and sodium oxybate, as well as lifestyle adjustments. *Id.* ¶ 12. Nevertheless, according to the Specification, due to side effects and other safety concerns associated with existing medications, "[t]here remains a need for effective treatments for narcolepsy." *Id.*

CLAIMED SUBJECT MATTER

The claims are directed to methods of treating narcolepsy. Claim 1, reproduced below, is illustrative of the claimed subject matter:

> 1. A method of treating narcolepsy comprising administering to a patient in need thereof a pharmaceutical composition comprising 4,5,6,7-tetrahydroisoxazolo [5,4-c] pyridine-3-ol (gaboxadol) or a pharmaceutically acceptable salt thereof.

Appeal Br. 11 (Claims App.).

REJECTIONS

A. Claims 1–10 are rejected under 35 U.S.C. § 103 as being unpatentable over Walsh[2] and Abad.[3]

[2] James K. Walsh et al., *Slow Wave Sleep Enhancement with Gaboxadol Reduces Daytime Sleepiness During Sleep Restriction*, 31 SLEEP 659 (2008).
[3] Vivien C. Abad & Christian Guilleminault, *New Developments in the Management of Narcolepsy*, 9 NATURE & SCIENCE OF SLEEP 39 (2017).

B. Claims 1–10 are rejected under 35 U.S.C. § 103 as being unpatentable over Walsh and Mignot.[4]

OPINION

A. Obviousness over Walsh and Abad (claims 1–10)

1. Issues

The Examiner finds Walsh teaches that gaboxadol (GBX) is a slow wave sleep (SWS) enhancing drug administered in a daily dose within the range of several of the instant claims. Final Act. 7. The Examiner finds that "Walsh does not teach a method of treating narcolepsy in a patient in need thereof with gaboxadol, as in the instant claims," but finds that Abad teaches that SWS-enhancers are effective to treat narcolepsy. *Id.* at 8. The Examiner determines that a skilled artisan "would have been motivated to use gaboxadol, taught by Walsh to be a slow-wave sleep (SWS) enhancer in patients with insomnia, in healthy patients and in human patients with sleep restriction, in a method to treat narcolepsy," with "the expectation of achieving a therapeutic effect," because "Abad teaches that SWS enhancers can be used to treat narcolepsy." *Id.* at 9.

Appellant contends that the combination of Walsh and Abad would not have provided a skilled artisan a reasonable expectation of success as to the claimed methods. Appeal Br. 3.

The issue with respect to this rejection is whether, in light of Walsh and Abad, a skilled artisan would have had a reasonable expectation of

[4] Emmanual Mignot & Seiji Nishino, *Emerging Therapies in Narcolepsy-Cataplexy*, 28 SLEEP 754 (2005).

success in treating narcolepsy by administering gaboxadol or a pharmaceutically acceptable salt thereof.

2. Findings of Fact

1. Walsh teaches that periods with more slow wave sleep (SWS), or its spectral power density counterpart, slow wave activity (SWA), "have been widely hypothesized to be a time of relatively heightened neurophysiological restoration or recuperation." Walsh 659, right col.; *see also id.* (stating that "[A] NUMBER OF INVESTIGATORS HAVE PROPOSED THAT INCREASED SLOW WAVE SLEEP . . . or slow wave activity . . . represent ongoing cortical recovery from prior wakefulness").

2. Walsh teaches that gaboxadol (GPX), "a selective (for $alpha_4$ delta receptors) extrasynaptic $GABA_A$ agonist," "has consistently increased SWS/SWA, in a dose-related manner, in adult and elderly healthy subjects and in primary insomnia patients." Walsh 660, left col.

3. Walsh "investigated the impact of enhanced SWS/SWA with GBX 15 mg on behavioral, psychological, and physiological changes resulting from sleep restriction." Walsh 660, left col.

4. Walsh reports that "SWS was consistently increased by GBX 15 mg during the 4-night sleep restriction period, relative to both baseline and to [placebo (PBO)] values." Walsh 668, left col.

5. Walsh reports that "the spectral power density changes seen with GBX are similar to those seen with homeostatic increases in sleep drive." Walsh 670, right col.

6. Walsh reports that

> [t]he placebo group displayed the predicted deficits due to due to sleep restriction on the multiple sleep latency test (MSLT) and on introspective measures of sleepiness and

> fatigue. Compared to placebo, the GBX group showed significantly less physiological sleepiness on the MSLT and lower levels of introspective sleepiness and fatigue during sleep restriction. There were no differences between groups on the psychomotor vigilance task (PVT) and a cognitive test battery, but these measures were minimally affected by sleep restriction in this study. The correlation between change from baseline in MSLT on Day 6 and change from baseline in SWS on Night 6 was significant in the GBX group and in both groups combined.

Walsh Abstract; *see also id.* at 669, left col.

7. Walsh concludes that "[t]he results of [its] study are consistent with the hypothesis that enhanced SWS, in this study produced by GBX, reduces physiological sleep tendency and introspective sleepiness and fatigue which typically result from sleep restriction." Walsh Abstract; *see also id.* at 668, right col. (stating the belief that increased SWS with GBX "represents an enhancement of at least some of the normal physiological processes associated with NREM sleep and is not simply an electroencephalographic change").

8. Walsh reports that in both this and a prior study, which used a different compound, tiagabine, SWS enhancement during sleep restriction "reduced the impact of sleep restriction on one or more metric known to be sensitive to sleep loss." Walsh 670, left col.

9. Walsh notes that its study failed to "show a beneficial effect of GBX on [psychomotor vigilance task (PVT)] performance," which "complicates interpretation of overall study results, especially since PVT performance was preserved during sleep restriction in similar study of SWS enhancement with tiagabine." Walsh 669, right col. However, Walsh

attributes this result to the mild deficit on PVT performance produced by the sleep restriction in the study, including in the placebo group. *Id.*

10. Walsh notes that "most investigations of selective deprivation of SWS or stage 4 alone have failed to support the concept of enhanced recuperative 'value' of SWS relative to other sleep stages," for instance because "[n]either performance nor alertness has been found to be impaired after reduction of SWS by approximately 25% to 90% relative to baseline." Walsh 659–660. However, Walsh attributes the negative findings of the studies to "[s]ignificant methodological limitations." *Id.*

11. An Editor's Footnote in Walsh notes that "[t]he clinical development program for gaboxadol was discontinued by Merck and Lundbeck because of an overall unfavorable therapeutic profile, including lack of efficacy in a three-month study and a higher incidence of psychiatric side effects." Walsh 659, left col.

12. Abad teaches that "[n]arcolepsy pathophysiology is linked to loss of signaling by hypocretin-producing neurons; an autoimmune etiology possibly triggered by some environmental agent may precipitate hypocretin neuronal loss." Abad Abstract.

13. Abad teaches that "[t]he narcolepsy pentad consists of excessive daytime sleepiness (EDS), cataplexy, hypnogogic hallucinations, sleep paralysis, and disrupted nocturnal sleep." Abad 40, left col.

14. Abad teaches that "[n]arcolepsy is associated with sleep fragmentation, frequent awakenings, and stage shifts; disrupted nocturnal sleep may add to daytime fatigue." Abad 52, left col.

15. Abad teaches novel SWS enhancers as one of the emerging therapies for narcolepsy that "may help consolidate disrupted night sleep." Abad 49, left col.

16. Abad teaches that, "[t]heoretically, drugs that promote slow-wave sleep could be helpful, but they have not undergone clinical trials for this indication, except for SXB." Abad 52, left col.

17. Abad teaches that "[s]odium oxybate (SXB) . . . is a first-line agent for cataplexy and EDS and may help sleep disruption, hypnagogic hallucinations, and sleep paralysis." Abad Abstract; *see also id.* at 41, bridging para. (teaching that SXB "may improve HH [(hypnagogic hallucination)] and SP [(sleep paralysis)]" and "help consolidate nocturnal sleep," that, "[c]ompared to placebo, SXB effectively reduced daytime sleepiness and improved cataplexy, and that "[s]leep attack frequency and duration were significantly reduced at 6 and 9 gram doses." *Id.*; *see also id.* at 52–53 (describing other studies relating to use of SBX to treat narcolepsy).

18. Abad teaches that tiagabine, another SWS enhancer, has "increased slow-wave sleep by 41% and improved ratings of the restorative nature of sleep." Abad 52, left col.

19. Abad teaches gaboxadol as another potential SWS enhancer. Abad 52, left col.

20. Abad teaches that "[m]ore research is needed to determine the usefulness of [other potential SWS enhancers] in consolidating nocturnal sleep in narcolepsy patients." Abad 52, left col.

21. Abad concludes that "[n]arcolepsy remains a complex disease whose cure remains elusive despite our expanding knowledge about its

pathophysiology" and that "[d]isease-specific therapies need further development and testing before they can be clinically relevant." Abad 54–55.

3. Analysis

We agree with Appellant that the Examiner has not established a prima facie case of the obviousness of the claims over Walsh and Abad, in particular with respect to the reasonable expectation of success of using gaboxadol in a method of treating narcolepsy.

The Examiner asserts that, "Abad clearly teaches . . . SWS enhancers and specifically teaches SWS enhancer garboxadol . . . as potential narcolepsy treatment." Ans. 8; *see also id.* at 10. More particularly, the Examiner asserts that "Abad . . . exemplif[ies] SWS-enhancer sodium oxybate as being effective in treating narcolepsy, and . . . clearly teach[es] gaboxadol, a SWS enhancer, could be helpful to treat narcolepsy." Ans. 11. The Examiner asserts that, thus, Abad "provide[s] much more than 'a hope': [it] provide[s] the motivation to test SWS enhancers, and gaboxadol specifically, in a method of treating narcolepsy; further, based on previous success in treating narcolepsy with other SWS enhancers, there is reasonable expectation of success." *Id.* The Examiner notes that "certainty is not required" to show obviousness and further notes that "patient population in the instant claims is not restricted to human patients" and that, in any event, "[e]fficacy in clinical trials is not a requirement for patentability." *Id.* at 8, 9. The Examiner asserts that "[t]he fact that narcolepsy can be treated using drugs having different mode of action/pharmacology, does not diminish in

any way the teaching by Abad . . . that drugs that promote slow-wave sleep can treat narcolepsy." Ans. 11.[5]

Although we understand the Examiner's position, and agree Abad teaches that sodium oxybate, a SWS enhancer, is effective in treating narcolepsy (FF17) and that other SWS enhancers, including gaboxadol, may be potentially useful in treating narcolepsy (FF15, FF16, FF18, FF19), we are not persuaded that the combination of Walsh and Abad provides a reasonable expectation that gaboxadol would be successful in the claimed method. Instead, the prior art merely renders gaboxadol obvious to try in a method to treat narcolepsy.

As our reviewing court has explained,

> [t]he admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988) (citations omitted).

[5] The Examiner asserts that, "[w]ithout testing gaboxadol in a relevant animal model of narcolepsy . . . , the observations in Thakkar are not relevant and cannot be extrapolated to the effectiveness of gaboxadol for treatment of narcolepsy." Ans. 13.

In this case, using gaboxadol to treat narcolepsy falls into at least the second category of obvious to try: That is, Abad discloses using SWS enhancers as a general approach that is promising in the field of narcolepsy treatment, for instance describing novel SWS enhancers as an *emerging* therapy for narcolepsy that "*may* help consolidate disrupted night sleep" and stating that, "*[t]heoretically*, drugs that promote slow-wave sleep *could* be helpful, but they have not undergone clinical trials for this indication, except for SXB." FF15, FF16 (emphasis added).

We agree with the Examiner that "certainty is not required" to show obviousness and that "[e]fficacy in clinical trials is not a requirement for patentability." Ans. 8, 9. Nevertheless, Abad does not provide *specific* guidance as to how gaboxadol may be used to treat narcolepsy, concluding instead that "[m]ore research is needed to determine the usefulness of [other potential SWS enhancers] in consolidating nocturnal sleep in narcolepsy patients," that "[n]arcolepsy remains a complex disease whose cure remains elusive despite our expanding knowledge about its pathophysiology," and that "[d]isease-specific therapies need further development and testing before they can be clinically relevant." FF20, FF21.

Accordingly, for the reasons discussed above, we reverse the Examiner's rejection of claims 1–10 as obvious over Walsh and Abad.

B. Obviousness over Walsh and Mignot (claims 1–10)

1. Issues

The Examiner finds Walsh teaches that gaboxadol (GBX) is a slow wave sleep (SWS) enhancing drug administered in a daily dose within the range of several of the instant claims. Final Act. 9. The Examiner finds that

"Walsh does not teach a method of treating narcolepsy in a patient in need thereof with gaboxadol, as in the instant claims," but finds that Mignot teaches that SWS-enhancers are effective to treat narcolepsy. *Id.* at 10. The Examiner determines that a skilled artisan "would have been motivated to use gaboxadol, taught by Walsh to be a slow-wave sleep (SWS) enhancer in patients with insomnia, in healthy patients and in human patients with sleep restriction, in a method to treat narcolepsy," with "the expectation of achieving a therapeutic effect," because "Mignot teaches that SWS enhancers can be used to treat narcolepsy." *Id.* at 11.

Appellant contends that the combination of Walsh and Mignot would not have provided a skilled artisan a reasonable expectation of success as to the claimed methods. Appeal Br. 3.

The issue with respect to this rejection is whether, in light of Walsh and Mignot, a skilled artisan would have had a reasonable expectation of success in treating narcolepsy by administering gaboxadol or a pharmaceutically acceptable salt thereof.

2. Findings of Fact

22. Mignot teaches that sodium oxybate, a slow-wave sleep-enhancing agent that consolidates nocturnal sleep, reduces cataplexy, and improves sleepiness, is useful in treating narcolepsy. Mignot Abstract; *see also id.* at 757, left col.

23. Mignot teaches that "[t]he mode of action of [sodium oxybate] is debated and may involve stimulation of GABA-B receptors and possibly other [sodium oxybate]-specific receptors." Mignot 754, right col.; *see also id.* at 757, left col.

24. Mignot teaches novel SWS enhancers as a future potential narcolepsy treatment. Mignot 756, Table 2. In particular, Mignot teaches that "[t]he efficacy of sodium oxybate . . . suggests that other hypnotics with SWS effect could have similar effects" and that "possible agents in this class could include novel GABA-B agonists, GABA-A subtype specific compounds such as gaboxadol, longer-acting [sodium oxybate] analogues, and GABA reuptake inhibitors such as tiagabine or others." *Id.*; *see also id.* at 757, right col. (noting that "[c]urrently studied or available GABAergic hypnotics with SWS-enhancing properties include gaboxadol, a GABAergic modulator with preferential effects on extrasynaptic GABAergic receptors containing the delta and alpha-4/5 subunits, and tiagabine, a GABA reuptake inhibitor") (endnote omitted).

25. More specifically, Mignot teaches that "[w]hether the SWS-enhancing property of [sodium oxybate], and the resulting decrease in homeostatic sleep debt, is needed for the beneficial effect of the compound on the various symptoms of narcolepsy is tantalizing" but that "[t]his question will only be answered when other compounds with similar SWS-enhancing profiles, but distinct molecular modes of action, will be available." Mignot 757, right col.

26. Mignot teaches that "[t]he existence of numerous other potential targets for hypnotics, such as 5-$HT_{2a/c}$ antagonists, histamine H_1 receptors antagonists, H_3 autoreceptor agonists, and ion channel blockers, together with the renewed interest of the pharmacologic sector in hypnotic therapies may also be beneficial to narcoleptic patients." Mignot 757, right col. Mignot teaches that "ritanserin, a 5-HT_2 receptor antagonist, has been

reported to have beneficial effects on disturbed nocturnal sleep in narcoleptic patients." *Id.*

3. Analysis

We agree with Appellant that the Examiner has not established a prima facie case of the obviousness of the claims over Walsh and Mignot, in particular with respect to the reasonable expectation of success of using gaboxadol in a method of treating narcolepsy.

The Examiner asserts that "Mignot clearly teaches . . . SWS enhancers as potential narcolepsy treatments," including exemplifying SWS-enhancer sodium oxybate as being effective in treating narcolepsy, and furthermore teaches gaboxadol as one of the two specific SWS enhancer compounds to be tested. Ans. 8, 11. The Examiner asserts that, thus, Mignot "provide[s] much more than 'a hope': [it] provide[s] the motivation to test SWS enhancers, and gaboxadol specifically, in a method of treating narcolepsy; further, based on previous success in treating narcolepsy with other SWS enhancers, there is reasonable expectation of success." *Id.* at 11. The Examiner asserts that "[t]he fact that narcolepsy can be treated using drugs having different mode of action/pharmacology, does not diminish in any way the teaching by . . . Mignot that drugs that promote slow-wave sleep can treat narcolepsy." Ans. 11; *see also id.* at 12 (asserting that "[t]he fact that Mignot also teaches that other hypnotics, besides gaboxadol, having different molecular modes of action, may also be beneficial to narcoleptic patients, does not diminish in any way the teaching by Mignot that ghaboxadol is a SWS enhancer to be evaluated in a method of treating narcolepsy").

Once again, although we understand the Examiner's position, and agree Mignot teaches that sodium oxybate, a SWS enhancer, is effective in treating narcolepsy (FF22) and that other SWS enhancers, including gaboxadol, may be potentially useful in treating narcolepsy (FF24), we are not persuaded that the combination of Walsh and Mignot provides a reasonable expectation that gaboxadol would be successful in the claimed method, for reasons similar to those discussed above with respect to the combination of Walsh and Abad.

In particular, Mignot teaches novel SWs enhancers only as a *future potential* narcolepsy treatment. FF24. Although it is the case that "the expectation of success need only be reasonable, not absolute," *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007), Mignot describes the question of "[w]hether the SWS-enhancing property of [sodium oxybate], and the resulting decrease in homeostatic sleep debt, is needed for the beneficial effect of the compound on various symptoms of narcolepsy" as "tantalizing," but explicitly teaches that the question "will only be answered when other compounds with similar SWS-enhancing profiles, but distinct molecular modes of action, will be available." FF25. Given the speculative nature of Mignot's statements with regard to the gaboxadol's potential for treating narcolepsy, we find that the combination of Walsh and Mignot may suggest that use of SWS enhancers such as gaboxadol is a "promising field of experimentation" for treating narcolepsy, but does not provide sufficient guidance so as to render the method obvious. *O'Farrell*, 853 F.2d at 903 (explaining that obviousness rejection is error where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general

guidance as to the particular form of the claimed invention or how to achieve it").

Accordingly, for the reasons discussed above, we reverse the Examiner's rejection of claims 1–10 as obvious over Walsh and Mignot.[6]

C. New ground of rejection — Lack of enablement (claims 1–10)

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following new ground of rejection: Claims 1–10 are rejected under 35 U.S.C. § 112(a) as lacking enablement.

1. Findings of Fact

Breadth of Claims

27. Claim 1 is drawn to a method of treating narcolepsy by administering gaboxadol, or a pharmaceutically acceptable salt of gaboxadol, to a patient in need thereof.

Presence of Working Examples

28. The Specification provides an example that shows "plasma concentration profiles and dose proportionality of gaboxadol monohydrate following single oral doses ranging from 2.5 to 20 mg" and assesses

[6] Appellant also argued that Thakkar teaches away from the claimed invention because Thakkar teaches that gaboxadol may induce inhibition of orexin neurons and also teaches that deficient or reduced orexinergic neurotransmission resulted in narcolepsy in humans. Appeal Br. 8–9. The Examiner asserts that, "[w]ithout testing gaboxadol in a relevant animal model of narcolepsy . . . , the observations in Thakkar are not relevant and cannot be extrapolated to the effectiveness of gaboxadol for treatment of narcolepsy." Ans. 13. We need not address this issue because, as discussed above, we find that the combination of Walsh and Mignot does not provide a skilled artisan with a reasonable expectation of success with respect to the claimed method of treating narcolepsy with gaboxadol.

"absolute bioavailability of gaboxadol monohydrate capsules ranging from 2.5 to 20 mg." Spec. ¶ 117.

29. However, the Specification does not contain any working examples regarding treatment of narcolepsy using gaboxadol.

Amount of Direction or Guidance Presented

30. The Specification teaches that gaboxadol is "a selective $GABA_A$ receptor agonist with a preference for δ-subunit containing $GABA_A$ receptors." Spec. ¶ 13.

31. The Specification generically teaches treating narcolepsy by administering gaboxadol to patients and discloses a wide range of dosages, dosage forms, routes of administration, and frequency of administration. For example, the Specification states:

> In embodiments, methods of treating narcolepsy include administering to a patient in need thereof a pharmaceutical composition including about 0.05 mg to about 50 mg gaboxadol or a pharmaceutically acceptable salt thereof. . . . In embodiments, as discussed below, various dosage forms including conventional formulations and modified release formulations can be administered one or more times daily. Any suitable route of administration may be utilized, e.g., oral, rectal, nasal, pulmonary, vaginal, sublingual, transdermal, intravenous, intraarterial, intramuscular, intraperitoneal and subcutaneous routes. Suitable dosage forms include tablets, capsules, oral liquids, powders, aerosols, transdermal modalities such as topical liquids, patches, creams and ointments, parenteral formulations and suppositories.

Spec. ¶ 26; *see also, e.g., id.* ¶¶ 27–29, 31–32. Similarly, the Specification teaches that "[i]n embodiments, the pharmaceutical compositions described herein are administered once, twice, or three times daily, or every other

day." *Id.* ¶ 30. The Specification teaches that "[t]he precise dosage can vary according to a variety of factors such as subject-dependent variables (*e.g.*, age, immune system health, clinical symptoms etc.)." *Id.* ¶ 75.

32. The Specification teaches that "[e]ffective treatment of narcolepsy herein . . . may be established by showing reduction in the frequency or severity of symptoms," such as "one or more of excessive daytime sleepiness, abnormal REM sleep, cataplexy, sleep paralysis, hallucinations, automatic behaviors and night-time wakefulness," after a period of time compared with baseline. Spec. ¶¶ 74–75.

33. The Specification teaches:

> [P]eople with narcolepsy frequently abnormally enter REM sleep within 15 minutes of falling asleep. Surprisingly, it has been found that administration of 0.5 mg to 25 mg of gaboxadol or a pharmaceutically acceptable salt thereof to a narcoleptic patient can delay onset of REM sleep to 30 minutes or more after falling asleep. Without wishing to be bound by any theory, symptoms associated with narcolepsy such as cataplexy, sleep paralysis, hallucinations, and automatic behaviors closely mimic the natural physiologic response that occurs during REM sleep. By inducing a more normal REM sleep architecture in narcoleptic patients, symptoms associated with narcolepsy are reduced or alleviated.

Spec. ¶ 76.

State of the Art, Unpredictability of the Art, and Quantity of Experimentation

34. *See* FF9–FF11, FF16, FF20, FF21, FF23, FF25.

35. Thakkar teaches that "[t]he γ-aminobutyric acid (GABA) system is closely linked with the regulation of sleep-wakefulness" and that, "[t]hus, it is not surprising that pharmacological landscape for treatment of

various sleep disorders including insomnia have been dominated by agents that activate $GABA_A$ receptors." Thakkar Abstract.

36. Thakkar teaches that "[t]here is strong evidence indicating that the [perifornical lateral hypothalamus (PFH)] is critical for wakefulness" and that "there is compelling and consistent evidence implicating the orexins neurons, [which may be found in PFH,] in the control of wakefulness." Thakkar 2.

37. Thakkar teaches that "local administration of orexin in various brain regions produced wakefulness," whereas "a deficiency or reduction of orexinergic neurotransmission resulted in a reduction in wakefulness and cataplexy like episodes in rodents . . . and narcolepsy in humans." Thakkar 2.

38. Thakkar teaches that "[n]umerous studies have shown that [gaboxadol] selectively activates the δ-subunit containing extrasynaptic $GABA_A$ receptors in the brain . . . and systemic administration of [gaboxadol], in rats and humans, increases nonREM sleep and reduces wakefulness without affecting REM sleep." Thakkar 4. However, Thakkar also teaches that "recent in *vivo* studies have shown that systemic [gaboxadol] administration does not promote sleep in mice." *Id.*

39. Thakkar teaches that its study shows that "[l]ocal unilateral administration of [gaboxadol] . . . in the PFH produced a significant increase in nonREM sleep with a concomitant reduction in wakefulness during the light period in freely behaving rats." Thakkar 4. In particular, Thakkar teaches that its study "suggests that unilateral administration of 100 μM [gaboxadol] into the PFH increased nonREM sleep and reduced wakefulness as compared to [artificial cerebrospinal fluid (ACSF)] perfusion" and that

"[t]his effect may be due to [gaboxadol] induced inhibition of orexin neurons because . . . orexinergic neurons are under GABAergic control during sleep although[] [gaboxadol] induced inhibition of other no-orexinergic neurons cannot be ruled out." *Id.*

40. Appellant contends that "in the case of narcolepsy, in view of Thakkar," a skilled artisan "would have reason to be concerned that administration of gaboxadol would increase episodes of cataplexy and exacerbate symptoms of narcolepsy." Appeal Br. 9.

41. The Specification states that "[i]n the 1990s gaboxadol moved into late stage development for the treatment of insomnia but failed to show significant effects in sleep onset and sleep maintenance in a three-month efficacy study," and "patients with a history of drug abuse who received gaboxadol experienced a steep increase in psychiatric adverse events." Spec. ¶ 13. The Specification states that, "[a]s a result of these negative results the development of gaboxadol was terminated." *Id.*

Skill in the Art

42. The cited art, with papers from medical doctors and researchers with doctorate degrees, suggests that the skill in the art is high.

2. Principles of Law

> Factors to be considered in determining whether a disclosure would require undue experimentation . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

3. Analysis

The analytical framework for determining whether claims fail to satisfy the enablement requirement balances the *Wands* factors to determine if undue experimentation would have been required to perform the reasonable scope of the claimed method at the time of filing of the Specification.

Claim 1 is a method drawn to the use of gaboxadol or its pharmaceutically acceptable salts to treat narcolepsy. FF27. Although the claim is relatively narrow in terms of the recited pharmaceuticals (gaboxadol or its pharmaceutically acceptable salts) and the disease treated (narcolepsy), the Specification not only lacks any working examples regarding treatment of narcolepsy using gaboxadol (FF29), but also provides only the most generic teachings regarding, e.g., the dosage, route, and/or timing or frequency of administration of the recited pharmaceuticals (FF31).

As to unpredictability of the art and the quantity of experimentation needed, the evidence of record shows that narcolepsy is "a complex disease whose cure remains elusive despite . . . expanding knowledge about its pathophysiology" (FF21) and that a significant quantity of experimentation would have been required to carry out the claimed method.

For example, Abad teaches that more research is needed to determine the usefulness of SWS enhancers other than sodium oxybate in consolidating nocturnal sleep in narcolepsy patients. FF20; *see also* FF21 (Abad stating that "[d]isease-specific therapies need further development and testing before they can be clinically relevant"). Mignot teaches that the modes of action of sodium oxybate is debated and that the question of whether that compound's SWS-enhancing property results in its beneficial effect on

narcolepsy "will only be answered when other compounds with similar SWS-enhancing profiles, but distinct molecular modes of action, will be available." FF25.

As another example, in contrast to the claimed method of treating narcolepsy with gaboxadol, Thakkar suggests that gaboxadol may induce inhibition of orexin neurons (FF39) and also teaches that "a deficiency or reduction of orexinergic neurotransmission *resulted* in . . . narcolepsy in humans" (FF37 (emphasis added)). Indeed, Appellant suggests in response to the Examiner's obviousness rejection over Walsh and Mignot that, "in the case of narcolepsy, in view of Thakkar," a skilled artisan "would have reason to be concerned that administration of gaboxadol would increase episodes of cataplexy and exacerbate symptoms of narcolepsy." FF40.

The unpredictability of the art of sleep science is further highlighted by Walsh, which teaches that gaboxadol consistently increased SWS during its sleep restriction study and that the results of the study are "consistent with the hypothesis that enhanced SWS . . . reduces physiological sleep tendency and introspective sleepiness and fatigue which typically results from sleep restriction." FF4, FF7. Nevertheless, as indicated in an editor's note in Walsh, a clinical development program for gaboxadol was discontinued "because of an overall unfavorable therapeutic profile, including lack of efficacy in a three-month study." FF11; *see also* FF41 (The Specification states that "[i]n the 1990s gaboxadol moved into late stage development for the treatment of insomnia but failed to show

significant effects in sleep onset and sleep maintenance in a three-month efficacy study," and its development was terminated.).[7]

As discussed above, we find no guidance in the Specification, in the form of working examples or otherwise, that would lessen the unpredictability discussed in the prior art. Accordingly, we find that the balance of the *Wand* factors, including the unpredictability of the art regarding treatment of narcolepsy, the large quantity of experimentation necessary, the minimal guidance in the Specification, and the absence of any working examples, weighed against the relatively limited claim breadth and the high skill level in the art, supports a conclusion that undue experimentation would have been required to enable the full scope of the instantly claimed invention. Accordingly, we enter a new ground of rejection of claims 1–10 as lacking in enablement under 35 U.S.C. § 112(a).

CONCLUSION

The Examiner's rejections of claims 1–10 as obvious over (A) Walsh and Abad and (B) Walsh and Mignot are reversed. We enter a new ground of rejection of claims 1–10 as lacking enabling disclosure under 35 U.S.C. § 112(a).

[7] We acknowledge that Walsh does not specifically discuss narcolepsy. Nevertheless, we find it to speak to the unpredictability of the relevant art in showing that an increase in SWS does not necessarily translate into therapeutic efficacy for specific sleep disorders.

DECISION SUMMARY

In summary:

Claim(s) Rejected	35 U.S.C. §	Reference(s)/ Basis	Affirmed	Reversed	New Ground
1–10	103	Walsh, Abad		1–10	
1–10	103	Walsh, Mignot		1–10	
1–10	112(a)	Enablement			1–10
Overall Outcome				1–10	1–10

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellant, WITHIN TWO MONTHS FROM THE DATE OF THE DECISION, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new Evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the prosecution will be remanded to the examiner. . . .

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. . . .

Further guidance on responding to a new ground of rejection can be found in the Manual of Patent Examining Procedure § 1214.01.

REVERSED; 37 C.F.R. § 41.50(b)