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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHRISTOPHER A. DADAS and
TAMER ABOUSHWAREB[1]

Appeal 2019-003280
Application 14/722,473
Technology Center 1600

Before DONALD E. ADAMS, ERIC B. GRIMES, and TAWEN CHANG, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a method for reducing bladder calculi formation associated with a bladder augmentation or bladder reconstruction surgical procedure, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE and enter a new ground of rejection under 37 C.F.R. § 41.50(b).

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[1] Appellants identify the Real Party in Interest as Allergan, Inc. (Br. 3.)

STATEMENT OF THE CASE

"Bladder augmentation, also called augmentation cystoplasty, is a surgical procedure to increase the size of the bladder. . . . Bladder augmentation, reconstruction, or diversion procedures are performed on patients who lack adequate bladder capacity, [have] high detrusor pressures, or have failed less invasive therapies for detrusor over activity." (Spec. ¶ 4.) "Bladder calculi are stones or calcified materials that are present in the bladder, usually when the urine becomes concentrated." (*Id.* ¶ 3.) "Increased calculi formation has been observed with bladder augmentation or bladder reconstruction surgical procedures." (*Id.*) According to the Specification, "[t]he present disclosure relates to methods for protecting against bladder augmentation-associated complications by reducing the occurrence of or preventing the formation of calculi using neurotoxins." (*Id.* ¶ 2.)

Claims 1–14 are on appeal. Claim 1, the sole independent claim, is illustrative and reproduced below:

> 1. A method for reducing bladder calculi formation associated with a bladder augmentation or bladder reconstruction surgical procedure in a patient in need thereof, the method comprising locally administering a composition comprising a therapeutically effective amount of a clostridial derivative to the patient.

(Br. 14 (Claims App.).)

The Examiner rejects claims 1–4, 7–9, 11, and 13 under 35 U.S.C. § 103 as being unpatentable over Linsenmeyer[2] and Veeratterapillay.[3] (Ans. 4.)

The Examiner rejects claims 1, 5–8, 10, and 12 under 35 U.S.C. § 103 as being unpatentable over Linsenmeyer, Veeratterapillay, and Brin.[4] (Ans. 9.)

The Examiner rejects claim 14 under 35 U.S.C. § 103 as being unpatentable over Linsenmeyer, Veeratterapillay, Brin, and Schmidt.[5] (Ans. 9.)

DISCUSSION

Issue

The same issues are dispositive for all of the Examiner's rejections; we therefore discuss them together.

The Examiner finds that Linsenmeyer teaches treating neurogenic detrusor overactivity (NDO) of the bladder by injecting botulinum toxin (BoNT) type A, a clostridial derivative, into the bladder wall. (Ans. 5; Br. 14 (Claims App.), claims 7–9.) The Examiner finds that Linsenmeyer also teaches that NDO causes bladder stones. (Ans. 5.) The Examiner finds that Linsenmeyer further teaches that "other traditional bladder management options for [NDO] include bladder augmentation." (*Id.*)

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[2] Todd A. Linsenmeyer, *Use of Botulinum Toxin in Individuals with Neurogenic Detrusor Overactivity: State of the Art Review*, 36 J. SPINAL CORD MED. 402 (2013).
[3] Rajan Veeratterapillay et al., *Augmentation Cystoplasty: Contemporary Indications, Techniques and Complications*, 29 INDIAN J. UROLOGY 322 (2013).
[4] Brin, US 9,144,600 B2, issued Sept. 29, 2015.
[5] Schmidt, US 7,455,845 B2, issued Nov. 25, 2008.

The Examiner finds that, "[r]egarding claim 1, Linsenmeyer does not teach any specific therapeutic dosage" and "is silent regarding administering botulinum toxin before bladder augmentation surgery." (*Id.*) With respect to the limitation regarding "therapeutically effective amount," the Examiner finds that "the selection of any specific therapeutic dosage is implied by Linsenmeyer" and "would amount to nothing more than routine experimentation that can be optimized on an individual patient basis." (*Id.* at 6–7.) The Examiner also finds that "Veeratterapillay implies methods of locally administering botulinum toxin for use in the treatment of bladder stones for a patient in need of a surgical bladder augmentation cystoplasty." (*Id.* at 5–6.)

The Examiner concludes that a skilled artisan would have been motivated to combine Linsenmeyer and Veeratterapillay to arrive at the invention of claim 1, with a reasonable expectation of success, because

> Linsenmeyer teaches that botulinum toxin is effective at treating symptoms of neurogenic detrusor overactivity which is causative of bladder stones/calculi and because both Linsenmeyer and Veeratterapillay . . . teach methods of bladder augmentation surgery can treat symptoms of neurogenic bladder overactivity. The skilled artisan would have been motivated to [administer BoNT type A before the bladder augmentation surgical methods of Veeratterapillay] because Veeratterapillay teaches that bladder augmentation cystoplasty may be required if intravesical botulinum toxin administration fails to relieve neurogenic or non-neurogenic bladder dysfunction.
> Alternatively. . . , the skilled artisan would have been motivated to do so because the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results . . . .

(*Id.* at 7.)

Appellants contend that the combination of cited prior art does not teach or suggest using BoNT "for reducing bladder calculi formation associated with a bladder augmentation or bladder reconstruction surgical procedure in a patient in need thereof," as required by independent claim 1. (Br. 7–12.)

The issue with respect to this rejection is whether a preponderance of evidence of record supports the Examiner's conclusion that, based on the combination of cited references, it would have been obvious to a skilled artisan to administer BoNT to a patient in need of the reduction of bladder calculi formation associated with a bladder augmentation or bladder reconstruction surgical procedure.

Findings of Fact

1. Linsenmeyer teaches that

> Botulinum neurotoxin (BoNT) injection into the bladder wall has been shown to be an effective alternative to anticholinergic (antimuscarinic) medications and more invasive surgery in those with multiple sclerosis and spinal cord injury with neurogenic detrusor overactivity (NDO) and urinary incontinence who are not tolerating anticholinergic medications. . . . Clinically, intradetrusor injection of BoNT has been found to decrease urinary incontinence and improve quality of life. Its impact on urodynamic parameters is an increase in the maximum cystometric (bladder) capacity and decrease in the maximum detrusor pressures. The most common side effects are urinary tract infections and urinary retention.

(Linsenmeyer Abstract; *see also id.* at 403, right column; 404, left column; 414, right column; and 415, left column.)

2. Linsenmeyer teaches that BoNT increases maximum bladder capacity and decreases maximum detrusor pressure (MDP) by suppressing

uninhibited bladder contractions and further teaches that "this may occur by decreasing the afferent input from bladder wall distention and may prevent and over time decrease bladder wall fibrosis." (*Id.* at 412, right column; 417, right column.)

3. Linsenmeyer teaches that "[o]ther traditional bladder management options for those . . . having problems with NDO include . . . bladder augmentation." (*Id.* at 403, right column.)

4. Linsenmeyer teaches that NDO may cause lower urinary tract complications such as bladder stones. (*Id.* at 403, left column.)

5. Veeratterapillay teaches that "[a]ugmentation cystoplasty (AC) has traditionally been used in the treatment of the low capacity, poorly compliant or refractory overactive bladder (OAB)" but that "[t]he use of intravesical botulinum toxin . . . in detrusor overactivity has reduced the number of AC performed for this indication." (Veeratterapillay Abstract.)

6. Veeratterapillay teaches that

> AC remains an option, with high patient satisfaction rates, in neurogenic and non-neurogenic bladder dysfunction when conservative management, pharmacological methods and minimally invasive treatments have been unsuccessful and exhausted. Patients with detrusor overactivity would initially undergo conservative measures with the addition of anticholinergic medications. If these are unsuccessful, the next step would be a trial of intravesical botulinum toxin medications or sacral neuromodulation. Patients who fail treatment with all those modalities are then considered for augmentation cystoplasty.

(*Id.* at 322.)

7. Veeratterapillay teaches that long-term problems of AC include urinary tract stones. (*Id.* at Abstract.) In particular, Veeratterapillay teaches

that "[b]ladder stones have been reported in up to 40% of AC and are thought to arise as a result of urinary stasis." (*Id.* at 325.)

Analysis

On balance, we find Appellants to have the better argument. In particular, while the combination of Linsenmeyer and Veeratterapillay teaches that both botulinum toxin (BoNT) and bladder augmentation are useful for treating detrusor overactivity (FF1–3, 5, 6) and that both detrusor overactivity and bladder augmentation may cause bladder stones (FF4, FF7), the Examiner has not persuasively explained how Linsenmeyer and Veeratterapillay suggest using BoNT to treat a patient having bladder augmentation.

Thus, while it may be obvious to administer BoNT to treat detrusor overactivity, which may in turn reduce bladder stone formation *associated with detrusor overactivity*, the Examiner has not established that it would be prima facie obvious to administer BoNT to a patient in need of bladder augmentation surgery in order to reduce bladder stone formation *associated with a bladder augmentation procedure*, as recited in claim 1.[6]

[6] We note that, to the extent a skilled artisan would have found it obvious to treat detrusor overactivity by both administering BoNT *and* performing bladder augmentation, the limitation of "reducing bladder calculi formation associated with a bladder augmentation or bladder reconstruction surgical procedure in a patient in need thereof" may be inherently met. However, both Linsenmeyer and Veeratterapillay appear to suggest that BoNT and bladder augmentation surgery are alternatives to each other (FF1, FF3, FF5, FF6) and Veeratterapillay appears to suggest that a patient may not be considered in need of bladder augmentation until he or she has failed treatment with BoNT. (FF6.) In any event, the Examiner has made no findings or conclusions with respect to whether the claim preambles may be

Accordingly, we reverse the Examiner's rejection of claim 1. We also reverse the rejections of claims 2–14, which depend from claim 1, for the same reasons.

REJECTION UNDER 37 C.F.R. § 41.50(b)

We make the following new ground of rejection using our authority under 37 C.F.R. § 41.50(b).

Claim 1 is rejected under 35 U.S.C. § 103 as obvious over Veeratterapillay and Schmidt.

Findings of Fact

8. Schmidt teaches that "[u]rinary rentention occurs when a patient cannot fully empty the bladder" and "may be either an acute or chronic condition." (Schmidt 1:46–48.)

9. Schmidt teaches that "[u]rinary retention may be due to an overactive bladder which is characterized by uncontrolled, frequent expulsion of urine from the bladder." (*Id.* at 1:56–58.)

10. Schmidt teaches that "[s]tones may form in the urinary tract of individuals with urinary retention caused by the stoppage of urine flow and/or infection." (*Id.* at 2:30–32.)

11. Schmidt teaches "methods for treating neurological-urological conditions, including urinary retention," by "administration of a botulinum toxin into the lower urinary tract of a patient with urinary retention,

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non-limiting or inherently met, and we decline to make such findings and conclusions in the first instance.

including the bladder or urinary sphincter and the bladder wall." (*Id.* at Abstract; *see also id.* at 5:14–17, 34–38, 46–53, 61–66; 7:42–47.)

12. Schmidt teaches that its method may relieve urinary retention as well as symptoms thereof. (*See, e.g., id.* at 7:15–18.)

13. Schmidt teaches that the appropriate dosage schedule for its method is "readily determined by one skilled in the art based on, e.g., patient size and the condition to be treated, and will depend on many factors, including the neurotoxin selected, the condition to be treated, the degree of irritation, and other variables." (*Id.* at 6:22–27.)

14. Schmidt teaches that

> [t]herapeutically effective amounts of botulinum toxin can be any amounts or doses that are less than a toxic dose, for example, less than about 3000 IU/70 kg male or about 43 IU per kg, preferably between 100 IU/70kg male or about 1.4 IU per kg, up to about 1200 IU/70 kg or about 17 IU per kg. Preferred amounts of botulinum toxin to administer includes amounts between about 20 IU per 70 kg male or about 0.3 IU per kg, amounts of about 30 IU per 70kg male or about 0.4 IU per kg, about 40 IU per 70 kg male or about 0.6 IU per kg, to about 100 IU per 70 kg male or about 1.4 IU per kg. The dosages can be given as a single dose, or as divided doses, for example, divided over the course of four weeks.

(*Id.* at 14:66–15:10.)

Analysis

Veeratterapillay teaches that formation of bladder stones is a long-term problem in bladder augmentation surgery and suggests that stones associated with such surgery may be caused by urinary stasis (i.e., urinary retention). (FF7.) Schmidt also teaches that urinary retention may cause urinary tract stones and further teaches that botulinum toxin administered

locally (e.g., to the bladder wall) may be used to treat urinary retention and/or its symptoms. (FF11, FF12.) Finally, Schmidt teaches that the appropriate dosage schedule for its method can be readily determined by a skilled artisan and further teaches a preferred therapeutically effective amount of botulinum toxin (e.g., 20–100 IU per 70 kg male) that overlaps with the claimed range (10 units to about 500 units). (FF13, FF14, Br. 14 (Claims App.), claim 10.)

In light of the combined teachings of Veeratterapillay and Schmidt, we conclude that a skilled artisan would have had reason to locally administer a composition comprising a therapeutically effective amount of a clostridial derivative (i.e., botulinum toxin) to a patient in need of reduction of bladder calculi formation associated with a bladder augmentation procedure, as recited in claim 1, with a reasonable expectation of success: Veeratterapillay suggested that bladder calculi formation associated with bladder augmentation surgery is caused by urine retention, and Schmidt teaches that local administration of botulinum toxin is useful for treating both urinary retention and its symptoms. Finally, the limitation relating to the "therapeutically effective amount" of the drug is prima facie obvious because the prior art teaches a range of therapeutically effective drug amounts that overlaps with claimed amounts, and the appropriate dosage of the drug (i.e., the "therapeutically effective amount") is further taught in the prior art as a routinely optimizable parameter.

SUMMARY

For the reasons above, we reverse the Examiner's decision rejecting claims 1–14.

In a new ground of rejection, we reject independent claim 1 under 35 U.S.C. § 103. We have not addressed Appellants' dependent claims, but in the event of further prosecution we leave it to the examiner to consider whether any of the dependent claims should also be rejected over the prior art.

TIME PERIOD FOR RESPONSE

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

> When the Board enters such a non-final decision, 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. The new ground of rejection is binding upon the examiner unless an amendment or new Evidence not previously of Record is made which, in the opinion of the examiner, overcomes the new ground of rejection designated in the decision. Should the examiner reject the claims, appellant may again appeal to the Board pursuant to this subpart.
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same Record. The request for rehearing must address any new ground of rejection and state with particularity the points believed to have been misapprehended or overlooked in

> entering the new ground of rejection and also state all other grounds upon which rehearing is sought.

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)