REVIEW ARTICLE

Conservative Treatment of Benign Prostatic Hyperplasia

Part 2 in a Series on Benign Prostatic Hyperplasia

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SUMMARY

Introduction: The rational pharmacological treatment of patients with symptomatic benign prostatic hyperplasia involves alpha blockers such as alfuzosin, doxazosin, tamsulosin and terazosin and 5-alpha reductase inhibitors such as dutasteride and finasteride. Methods: Selective literature review. Results: Alpha blockers are characterized by a rapid onset of action and superior symptom control. All alpha blockers display comparable effects, but quantitative differences exist in their side effect profiles. Alfuzosin and tamsulosin seem to be better tolerated than other drugs, particularly in patients with cardiovascular comorbidity and/or those receiving vasoactive comedications. 5-alpha reductase inhibitors have a slower onset of action, are only effective in patients with large prostates, and lead to less improvement in symptoms than alpha blockers. On the other hand, only 5-alpha reductase inhibitors reduce prostate size and long-term complications such as acute urinary retention. Combination treatment with both drug classes is superior to either monotherapy, but this manifests only after long term treatment. Since adverse events are also additive, combination treatment is primarily indicated for patients with a high risk of progression. Discussion: New data on progression and risk estimates allow a more targeted patient selection, particularly for the use of combination treatment.

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Key words: prostatic hyperplasia, therapeutic approach, alpha blocker, finasteride, tamsulosin

Benign prostatic hyperplasia (BPH) is primarily a histological diagnosis (1); in its clinical presentation, BPH includes both obstructive and irritative symptoms. The former, such as weak urinary stream, manifest during micturition, whereas the latter, such as pollakisuria, urinary urgency, and nocturia, manifest during the storage phase of the micturition cycle. In most patients, it is the irritative symptoms that have a greater impact on well-being and quality of life. Although clinical BPH is a chronic, progressive disease, the prognosis differs from patient to patient. Symptoms do not worsen in all patients, but often fluctuate over the course of disease, at times remaining constant or even showing spontaneous improvement (2). The major risk factors for progression are non-cancer-related high prostate-specific antigen (PSA) levels, large prostate volumes, and severe initial symptoms (3).

A number of options are available for treating clinical BPH, all of which vary in their effectiveness, invasiveness, and, thus, tolerability. Currently, the most effective forms of treatment are the most invasive. As a result, treatment must be specific to each patient and based on an individual assessment of benefits and risks. The choice of treatment depends on the goal of treatment. Some patients have only mild symptoms and seek medical help primarily because of their fear of cancer. In these cases, the chief goal should be to rule out the presence of malignancies and provide the patient with appropriate medical advice. If cancer has been ruled out and the patient's symptoms and distress are minimal, watchful waiting and monitoring may be the best approach. The most common reason for seeking medical care, however, is the patient's wish to alleviate the symptoms of BPH. Here, it is important that the invasiveness of treatment be proportionate to the severity of symptoms and the patient's degree of suffering. Another goal of treatment can be to stop the disease from progressing, thus preventing future morbidity, especially in patients at a high risk of

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progression. These different indications are important to keep in mind when choosing the most appropriate form of treatment. This paper describes the specific advantages and disadvantages of individual treatment options, drawing upon the clinical and scientific experience of the authors, a selective review of recent literature, and guidelines for the management of clinical BPH published by the German Urological Association (4) and the European Association of Urology (5).

Any comparative evaluation of treatment methods depends on being able to quantify both symptoms and therapeutic success. In the case of BPH, however, quantitative evaluation is difficult. In almost all of the double-blind studies conducted to date, randomization was preceded by a single-blinded placebo phase. Although symptoms already improved during this phase, the reported baseline data were not collected until after this phase had been completed. Moreover, the clear improvement in symptoms typically seen in the placebo group is primarily due to the fact that the outcome parameter is also the inclusion criterion – in other words, the fluctuating symptoms of BPH lead to regression towards the mean. In this regard, it is hardly surprising that the reduction in symptoms reported in open-label studies (without a single-blinded phase) is often almost twice as high as those seen in randomized, double-blind studies. Comparisons between different forms of treatment should thus be interpreted with caution if they are not part of direct comparative studies.

The following review will focus primarily on alpha-adrenergic antagonists (i.e. alpha blockers) and 5-alpha reductase inhibitors, because these are the only two drug classes for which sufficient data in the treatment of clinical BPH are available. Indeed, for all of the currently available agents in both drug classes, multiple high-quality, randomized, placebo-controlled double-blind studies and systematic meta-analyses have been conducted to date, ensuring that the criteria for level 1 evidence are met. Considering the frequent fluctuations in the severity of symptoms observed in BPH and the fact that approximately one-third of patients do not respond well to treatment, re-assessment and evaluation using a validated instrument such as the International Prostatic Symptom Score (IPSS) are recommended to determine a patient's response to a particular approach.

Alpha blockers

Alpha blockers act on alpha-1 adrenergic receptors in the prostate and urethra, leading to smooth-muscle relaxation. It is thought that these agents may also affect receptors in the bladder and/or spinal cord (6). The alpha-1A subtype is predominantly expressed in the prostate and urethra, whereas in the bladder and spinal chord the alpha-1D subtype is also present. Although alpha blockers have only a limited impact on bladder outlet resistance, they do reduce both the irritative and obstructive symptoms of BPH and show beneficial effects regardless of whether these symptoms are mild, moderate, or severe. In open-label studies, alpha blockers have led, on average, to an approximately 70% reduction in symptoms. The onset of action occurs within hours or days of achieving the target dose,

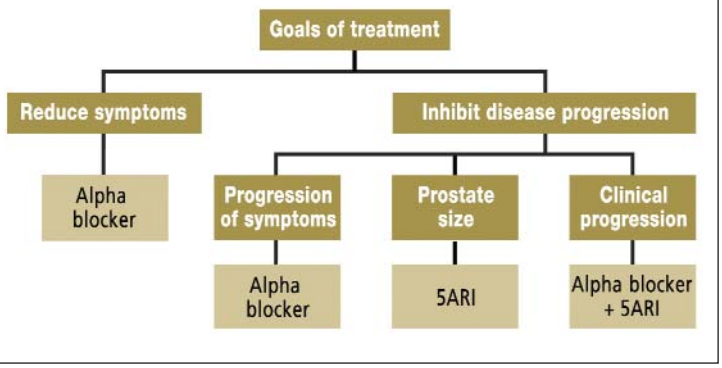
TABLE

Effective doses of alpha blockers and 5-alpha reductase inhibitors in the treatment of BPH

Agent	Dose (mg/day)
Alpha blockers	
Alfuzosin	1 x 10
Doxazosin *1,2	1 x 4–8
Tamsulosin *1	1 x 0.4
Terazosin *2	1 x 5–10
5-alpha reductase inhibitors	
Dutasteride	1 x 0.5
Finasteride	1 x 5

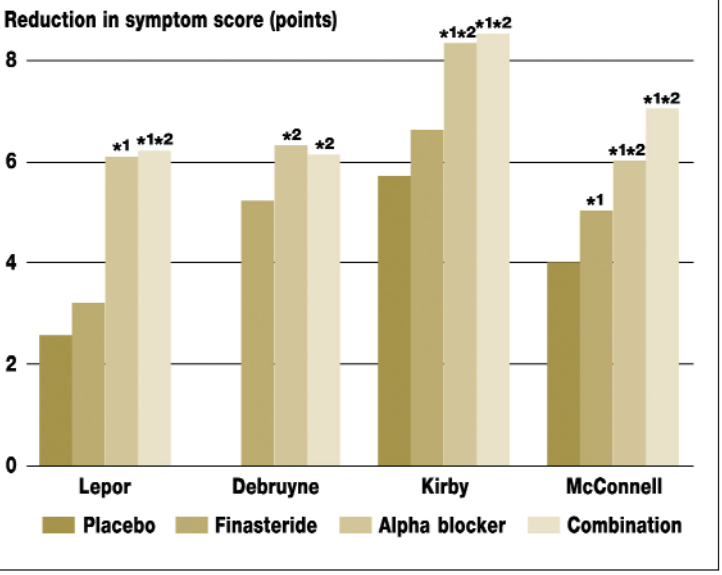
*1 This dose applies to both of the currently available formulations
*2 In studies in which upward titration was possible, more than half of the participants were receiving the higher dose by the end of the study.

DIAGRAM 1



Schematic representation of different indications for use of alpha blockers and 5-alpha reductase inhibitors (5ARIs) in the management of symptomatic benign prostatic hyperplasia

DIAGRAM 2



Comparison of symptom score reduction through treatment with alpha blockers and 5-alpha reductase inhibitors. The data from Debruyne et al. reflect 6 months, McConnell et al 48 months, and the two other studies 12 months of treatment.*1 and *2: $p < 0.05$ versus placebo and finasteride, respectively. In each case, the success of treatment was measured using disease-related, validated symptom scores, such as the International Prostate Symptom Score. Adapted from Lepor et al. (18), Debruyne et al. (19), Kirby et al. (20), and McConnell et al. (7).

and these agents have demonstrated a sustained efficacy of at least 4 to 6 years (7, 8). Nevertheless, although alpha blockers prevent the progression of symptoms, they do not inhibit prostate growth. As a result, this class of drugs does not prevent long-term complications such as acute urinary retention (7).

Currently, a total of 4 alpha blockers – some in multiple pharmaceutical formulations – are approved in Germany for the treatment of clinical BPH: alfuzosin, doxazosin, tamsulosin, and terazosin. Indirect comparisons between studies of different agents, as well as direct comparative studies, have shown that all alpha blockers have comparable efficacy when administered at the appropriate doses (9). When doses lower than those listed in the *table* are administered due to tolerability issues, however, comparable efficacy can no longer be assumed (10).

Alpha blockers are well tolerated in general. Typical side effects include dizziness and hypotension, which are assumed to result from the vascular effects of these drugs and are

more common for doxazosin and terazosin, which were developed primarily for the treatment of high blood pressure, than they are for alfuzosin and tamsulosin, which are approved specifically for the treatment of BPH (9). From a clinical perspective, these side effects are particularly relevant in patients who have cardiovascular comorbidities and/or are taking vasoactive comedications, including not only blood pressure medication, but also the phosphodiesterase type 5 inhibitors used to treat erectile dysfunction (11). Although tamsulosin has been shown to have a superior cardiovascular safety profile, it is also more likely to cause abnormal ejaculation than the other alpha blockers; in direct comparative studies, however, the differences between the various agents in this class have usually not been statistically significant (12).

Doxazosin and tamsulosin are available in various pharmaceutical formulations that differ in their release characteristics, but not in their clinical effectiveness. The new formulations, however, have certain advantages with regard to tolerability, especially in patients at an increased risk of experiencing side effects. Physicians will need to decide in each individual case whether these advantages justify possible differences in cost.

These data show that alpha blockers are indicated for the control of BPH symptoms (4, 5) *(diagram 1)*. These agents can even be used to manage severe symptoms when patients are reluctant to undergo surgical treatment, although caution is advised in cases of severe obstruction. Considering the frequency with which the symptoms of BPH can fluctuate, short term or intermittent treatment is another option. The choice of which alpha-blocker to use depends, for the most part, on the particular side-effect profile of each agent, especially in patients who have cardiovascular comorbidities and/or are taking vasoactive comedications.

5-alpha reductase inhibitors

5-alpha reductase is an enzyme that catalyzes the conversion of testosterone to dihydrotestosterone, which is responsible for many androgenic effects in the prostate (13). In BPH patients, treatment with 5-alpha reductase inhibitors leads to a partial involution of the prostate (i.e. in the order of 20% to 25%) accompanied by an improvement in symptoms. Based on this mode of action, it can take from 3 to 6 months to achieve the full therapeutic effect. This effect has been shown to persist for at least 4 to 6 years (7). Meta-analyses have demonstrated that 5-alpha reductase inhibitors lead to a significant reduction in BPH symptoms over placebo only in men with prostate volumes $\geq$ 40 ml (14). A number of direct comparative studies have shown that the degree of symptom control achieved by 5-alpha reductase inhibitors is lower than that observed in patients treated with alpha blockers *(diagram 2)*. However, in contrast to alpha blockers, 5-alpha reductase inhibitors reduce the size of the prostate, which in long-term studies has been shown to prevent complications such as acute urinary retention and the need for surgery (15, 7).

5-alpha reductase inhibitors are generally well tolerated, but sexual side effects such as impotence or decreased libido can occur (16, 17). Moreover, treatment with 5-alpha reductase inhibitors leads to an approximately 50% reduction in serum PSA levels, which needs to be taken into account when screening for prostate cancer.

Currently, two 5-alpha reductase inhibitors have been approved in Germany: dutasteride and finasteride. They differ in that finasteride selectively inhibits the type 2 isoform of 5-alpha reductase, which is essential for prostate growth and function, whereas dutasteride inhibits both the type 1 and type 2 isoforms. The function of the type 1 isoform is unknown (13). The two drugs also differ with regard to their half-lives (i.e. 6 hours for finasteride compared to 3 to 5 weeks for dutasteride). Neither of these differences appears to be of clinical relevance, since both an indirect comparison of individual studies and a direct comparative study of both agents failed to reveal any substantial differences in efficacy or tolerability. These data have not been peer-reviewed and are accessible only through a company website (www.gsk.com).

5-alpha reductase inhibitors are primarily indicated to improve the prognosis of patients at high risk of disease progression *(diagram 1)* and entail long-term treatment. Thus, in contrast to alpha blockers, there is no rationale for short-term or intermittent therapy with these agents. In patients at low risk of disease progression and in whom the primary focus of treatment is symptom control, 5-alpha reductase inhibitors may nevertheless be indicated in cases in which alpha blockers cannot be used (e.g. due to severe side effects).

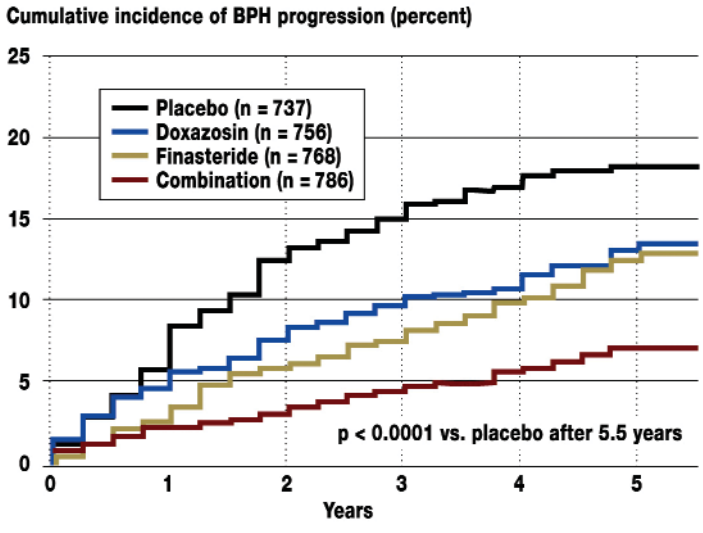
Combination treatment

Due to the complementary modes of action of alpha blockers and 5-alpha reductase inhibitors, combination therapy with both agents would appear to be an attractive approach and has been tested in a number of large studies (7, 18, 19, 20). These investigations demonstrated, however, that combination treatment over periods of up to 12 months has no advantages over monotherapy with an alpha-blocker *(diagram 2)*. The only study with an observation period of more than one year showed that long-term combination therapy had beneficial additive effects in inhibiting the clinical progression of BPH (7) *(diagram 3)*. Although these data were based on a combination of doxazosin plus finasteride, a class effect is assumed in each case. Despite the beneficial additive effects of combination therapy over the long term, it is important to consider the additional side-effects and increased costs associated with this treatment strategy. Indeed, the risk-benefit ratio suggests that combination treatment is primarily indicated in patients at a high risk of progression. In these patients, in particular, it is advisable to consider surgical (incl. minimally invasive) treatment, especially in cases where severe obstruction is present. At any rate, combination treatment is only indicated for patients in whom long-term, continuous therapy is planned; there is currently no evidence to support the use of intermittent combination treatment.

Alternative treatments

Plant extracts have long been a popular treatment for clinical BPH, particularly in Germany. Although their costs are no longer reimbursed by public health insurance funds in this country, German doctors are still frequently asked about these substances by their patients. Popular preparations include extracts from the fruits of saw palmetto (Sabal serrulata), from the roots of stinging nettle (Urtica dioica), from pumpkin seeds (Cucurbita pepo), and from rye pollen (Secale cereale), as well as plant sterols such as beta-sitosterol. Although there are positive study results for some of these (4), it is virtually impossible to draw firm conclusions about the efficacy and tolerability of any of the preparations available in Germany. It is in the nature of plant extracts and their production and processing that two extracts from the same plant will not necessary have the same effect. As a result, each phytopharmaceutical preparation must be evaluated separately; however, in most cases, only one study has been conducted for any single preparation. In addition, many of the

DIAGRAM 3



Comparison of the effects of the alpha blocker doxazosin and the 5-alpha reductase inhibitor finasteride on the clinical progression of BPH. In this study, clinical progression was defined as a worsening of symptoms, acute urinary retention, incontinence, recurrent urinary tract infections/urosepsis, or renal insufficiency. Adapted from (7), courtesy of Massachusetts Medical Society, USA.

available studies are not sufficiently robust, failing to conform to internationally accepted criteria in terms of patient numbers, treatment duration, or endpoints. Moreover, true blinding is often difficult. In the case of saw palmetto extracts, for example, the preparations have a characteristic smell. Most studies of preparations like these do not address the implications of such problems in blinding and thus may not represent true double-blind investigations. A recently published independent study that met all modern standards found no evidence supporting the efficacy of a saw palmetto extract over placebo (21). Although there is some indication that certain phytopharmaceuticals may be effective in the treatment of BPH, the currently available data are too limited to recommend their use.

It should be noted that common BPH symptoms such as pollakisuria, urinary urgency, and nocturia are also typical of overactive bladder syndrome (OAB). The standard treatment for OAB consists of muscarine receptor antagonists (22), but because of the possible risk of urinary retention, this class of agents is contraindicated in patients with bladder outlet obstruction. This being said, recent data indicate that the risk of urinary retention in BPH patients receiving treatment with muscarine receptor antagonists is possibly lower than previously thought (23). Thus, it may be feasible to use this class of agents in the management of BPH, in particular in patients with primarily irritative, rather than obstructive, symptoms. This approach is currently the subject of intense research, and the first pilot data appear promising (24). Nevertheless, the routine use of muscarine receptor antagonists in patients with BPH cannot yet be recommended, especially in cases where bladder outlet obstruction has not been ruled out.

Conclusion

In many patients the pharmacological treatment of BPH with alpha blockers and/or 5-alpha reductase inhibitors leads to adequate symptom control and is thus a reasonable alternative, in these cases, to surgical treatment, at least in the short to medium term. 5-alpha reductase inhibitors are less effective at controlling symptoms, but have a greater impact on the prostate growth underlying long-term disease progression.

Conflict of Interest Statement
Prof. Michel has received research grants, consulting fees, or speaker's fees from Astellas, Boehringer Ingelheim, Pfizer and Schwarz Pharma. Dr. Madersbacher has received lecture fees from MSD, GlaxoSmithKline, and Boehringer. Prof. Muschter has been reimbursed for lecturing activities and travel costs by GlaxoSmithKline, Wavelight, ProstaLund, Lilly, Pfizer and Misonix. Dr. Berges and Prof. Dreikorn declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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REFERENCES

1. Berges RR, Dreikorn K, Höfner K et al.: Leitlinien der Deutschen Urologen zur Diagnostik des benignen Prostatasyndroms (BPS). Urologe A 2003; 42: 584–90.
2. Emberton M, Andriole GL, de la Rosette JJMCH et al.: Benign prostatic hyperplasia: a progressive disease of aging men. Urology 2003; 61: 267–73.
3. Jimenez-Cruz F: Identifying the patients at risk for disease progression. Eur Urol Suppl 2003; 2: 6–12.
4. Berges RR, Dreikorn K, Höfner K et al.: Leitlinien der Deutschen Urologen zur Therapie des benignen Prostatasyndroms. Urologe A 2003; 42: 722–38.
5. Madersbacher S, Alivizatos G, Nordling J, Sanz CR, Emberton M, de la Rosette JJMCH: EAU 2004 Guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH Guidelines). Eur Urol 2004; 46: 547–54.
6. Michel MC, Vrydag W: α_1-, α_2- and β-adrenoceptors in the urinary bladder, urethra and prostate. Br J Pharmacol 2006; 147: S88–119.
7. McConnell JD, Roehrborn CG, Bautista O et al.: The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003; 349: 2387–98.
8. Narayan P, Evans CP, Moon T: Long-term safety and efficacy of tamsulosin for the treatment of lower urinary tract symptoms associated with benign prostatic hyperplasia. J Urol 2003; 170: 498–502.
9. Djavan B, Chapple C, Milani S, Marberger M: State of the art on the efficacy and tolerability of alpha$_1$-adrenoceptor antagonists in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia. Urology 2004; 64: 1081–8.
10. Berges RR, Michel MC, Jonas U: α_1-Rezeptorenblockade zur Therapie des BPH-Syndroms. Richtige Dosierung für optimale Wirkung. Urologe A 2002; 41: 452–7.
11. Barendrecht MM, Koopmans RP, de la Rosette JJMCH, Michel MC: Treatment for lower urinary tract symptoms suggestive of benign prostatic hyperplasia: the cardiovascular system. BJU Int 2005; 95 (Suppl. 4): 19–28.

12. van Dijk MM, de la Rosette JJMCH, Michel MC: Effects of α_1-adrenergic receptor antagonists on male sexual function. Drugs 2006; 66: 287–301.
13. Andriole G, Bruchovsky N, Chung LWK et al.: Dihydrotestosterone and the prostate: the scientific rationale for 5α-reductase inhibitors in the treatment of benign prostatic hyperplasia. J Urol 2004; 172: 1399–403.
14. Boyle P, Gould AL, Roehrborn CG: Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. Urology 1996; 48: 398–405.
15. McConnell JD, Bruskewitz R, Walsh P et al.: The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. N Engl J Med 1998; 338: 557–63.
16. Edwards JE, Moore RA: Finasteride in the treatment of clinical benign prostatic hyperplasia: a systematic review of randomised trials. BMC Urology 2002; 2: 14.
17. Evans HC, Goa KL: Dutasteride. Drugs Aging 2003; 20: 905–16.
18. Lepor H, Williford WO, Barry MJ et al.: The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. N Engl J Med 1996; 335: 533–9.
19. Debruyne FM, Jardin A, Colloi D et al.: Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia. Eur Urol 1998; 34: 169–75.
20. Kirby R, Roehrborn CG, Boyle P et al.: Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology 2003; 61: 119–26.
21. Bent S, Kane C, Shinohara K et al.: Saw palmetto for benign prostatic hyperplasia. N Engl J Med 2006; 354: 557–66.
22. Herbison P, Hay-Smith J, Ellis G, Moore K: Effectiveness of anticholinergic drugs compared with placebo in the treatment of overactive bladder: systematic review. BMJ 2003; 326: 841–4.
23. Abrams P, Kaplan S, de Koning Gans HJ, Millard R: Safety and tolerability of tolterodine for the treatment of overactive bladder in men with bladder outlet obstruction. J Urol 2006; 175: 999–1004.
24. Lee JY, Kim HW, Lee SJ, Koh JS, Suh HJ, Chancellor MB: Comparison of doxazosin with or without tolterodine in men with symptomatic bladder outlet obstruction and an overactive bladder. BJU Int 2004; 94: 817–20.

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