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Deprescribing Dual Therapy in Benign Prostatic Hyperplasia: A Patient Case

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Abstract

Background: Benign prostatic hyperplasia is a common condition affecting men worldwide that often requires the use of multiple medications. Older men may already be on several other medications for a variety of chronic conditions leading to a high prevalence of polypharmacy. Deprescribing is one approach to reduce polypharmacy, particularly if a medication is found to be high risk or no longer of benefit.

Case report: A 68 year-old male, with a past medical history of benign prostatic hyperplasia, acid reflux, hyperlipidemia, major depressive disorder, blindness, low body-mass index, and frailty was prescribed several medications including tamsulosin and finasteride. The clinical pharmacist noted that the patient had been prescribed this dual therapy for benign prostatic hyperplasia since 2015. Amongst other recommendations, the clinical pharmacist suggested deprescribing the alpha-blocker due to several factors including duration of use; potential risk of adverse events secondary to multi-drug interactions; and presence of polypharmacy. Once the recommendation was implemented, the patient reported no instances of increased lower urinary tract symptoms and was well maintained on monotherapy.

Conclusion: In patients with polypharmacy, the reduction of one medication may provide significant benefits. In the case of benign prostatic hyperplasia, patients who received six to twelve months of dual therapy may be able to control this condition with a 5-alpha-reductase inhibitor monotherapy. This class of medications has reportedly slowed clinical disease progression, reduced the risk of acute urinary retention and the need for invasive therapy, and improved voiding and storage symptoms. Healthcare providers should continue the practice of assessing medication regimens for appropriateness of therapy and deprescribing inappropriate therapy.

Keywords: Deprescribe • Benign prostatic hyperplasia • Dual therapy • Monotherapy • Geriatrics • Geriatric care

Abbreviations: BPH: Benign Prostatic Hyperplasia • LUTS: Lower Urinary Tract Symptoms • 5-ARI: 5-Alpha Reductase Inhibitors • MDI: Multi-Drug Interaction • ADE: Adverse Drug Event

Introduction

Benign Prostatic Hyperplasia (BPH) is a common condition affecting men worldwide. The prevalence of BPH increases with age, from approximately 15% to 35% in men aged 40 to over 80, respectively [1]. Men with BPH present with an enlargement of the prostate gland, often resulting in bladder obstruction and Lower Urinary Tract Symptoms (LUTS). LUTS may present as voiding complications (e.g., intermittent urine stream, hesitancy, straining) or storage complications (e.g., frequency, urgency, nocturia). BPH, due in part to LUTS, can significantly and negatively affect the quality of life in millions of men [1]. Alpha-adrenergic blockers (alpha-blockers) are the preferred class of medications to manage LUTS secondary to BPH [2]. Monotherapy with alpha-blockers (e.g., tamsulosin, alfuzosin, doxazosin) may be considered for mild symptoms; however, patients with moderate to severe symptoms may have greater benefits with 5-Alpha-Reductase Inhibitors (5-ARI) [2]. While alpha-blockers provide immediate therapeutic effects by relaxing smooth muscle in the bladder, 5-ARIs (dutasteride, finasteride) target the underlying disease progression and require approximately six to twelve months for therapeutic effects to manifest [2]. Due to these complementary mechanisms, patients will often be prescribed dual therapy with an alpha-blocker and a 5-ARI drug. Older patients may be on several medications for a variety of chronic conditions, leading to a high prevalence of polypharmacy in this population [3,4]. Polypharmacy increases out-of-pocket costs and increases the risk of Adverse Drug Events (ADEs), Multi-Drug Interactions (MDIs), and non-adherence [3,4]. Deprescribing is one approach to reduce polypharmacy in geriatric patients, particularly if a medication is found to be high risk or no longer necessary [3-5]. This case study describes a patient who was able to successfully discontinue an alpha-blocker after being maintained on dual therapy for several years.

Case Presentation

A 68-year-old male, with a past medical history of BPH, acid reflux, hyperlipidemia, major depressive disorder, blindness, low body-mass index, and frailty was scheduled for a comprehensive medication review. The review, conducted by a clinical pharmacist working closely with the patient's care team, included a thorough evaluation of the patient's medication regimen from the facility's electronic medical records and utilization of proprietary software to identify MDIs (Figure 1). Along with several other medications (Table 1), the clinical pharmacist noted that the patient had been prescribed dual therapy with tamsulosin and finasteride since 2015. The clinical pharmacist suggested deprescribing the alpha-blocker due to several factors including duration of use; lack of symptoms; potential risk of ADEs secondary to MDIs (Figure 1); and the presence of polypharmacy. The members of the patient care team accepted these recommendations and, upon follow-up with the providers after discontinuation, the patient denied symptoms of decreased flow and difficulty emptying his bladder. After discontinuing the tamsulosin, the reported prostate specific antigen was 0.3 ng/mL (reference range 0 to 4.5 ng/mL). Thirteen months later, the patient's condition is maintained on monotherapy with finasteride.

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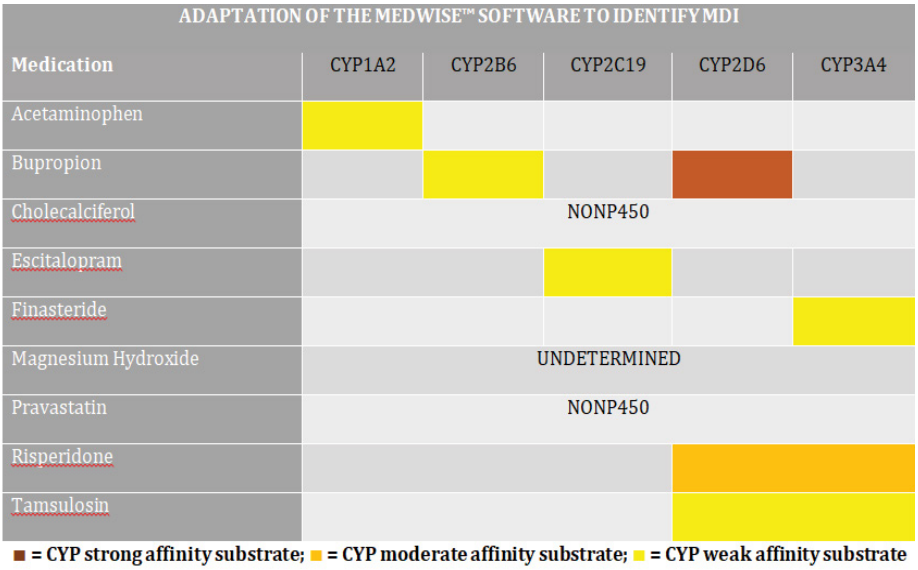

Figure 1. Electronic medical records and utilization of proprietary software to identify MDIs.

Table 1. Electronic medical records and utilization of proprietary software to identify MDIs along with several other medications.

Medication/Strength	Directions
Acetaminophen 650 mg	1 tablet every six hours as needed
Bupropion 100 mg	1 tablet once daily
Cholecalciferol 2000 I.U.	1 tablet once daily
Escitalopram 20 mg	1 tablet once daily
Finasteride 5 mg	1 tablet once daily
Magnesium Hydroxide 400 mg/5 mL	30 mL once daily as needed
Pravastatin 20 mg	1 tablet once daily
Risperidone 0.5 mg	1 tablet once daily
Tamsulosin 0.4 mg	1 tablet once daily

Discussion

This case serves as a reminder that medication appropriateness should be evaluated at every patient encounter. Furthermore, alpha-blockers, when part of a dual therapy regimen, can successfully be deprescribed without exacerbating symptoms of BPH after a certain period of time [6,7]. While the American Urological Association states there is insufficient information to deprescribe an alpha-blocker in individuals treated with dual therapy [2], the European Association of Urology states that after six months of dual therapy, the alpha-blocker may be deprescribed [6]. Additionally, the Dutch general practitioners advise that alpha-blockers be discontinued after three to six months, followed by routine symptom review [7].

These recommendations came about from three landmark clinical trials: the Medical Therapy of Prostatic Symptoms (MTOPS), the Symptom Management after Reducing Therapy (SMART-1), and the Combination of Avodart® and Tamsulosin (CombAT) study. The MTOPS study evaluated the long-term effects of monotherapy with an alpha-blocker (doxazosin) or 5-ARI (finasteride) or combined therapy [8]. This study demonstrated that all three options reduced the risk of overall clinical progression of BPH over a 4.5 year period, with the greatest reduction seen while utilizing dual therapy [8]. When compared to placebo, ADEs found to be clinically and statistically significant for doxazosin included dizziness, postural hypotension, and asthenia; in the finasteride group, patients reported erectile dysfunction, decreased libido and abnormal ejaculation at higher rates which were found to be clinically and statistically significant [8].

Though it was not found to be statistically significant, a higher percentage of men discontinued doxazosin compared to finasteride due to ADEs [8]. Ultimately, results indicated combination therapy and monotherapy with 5-ARIs were safe. Both reduced the risk of acute urinary retention, the need for invasive therapy, and the clinical progression of BPH compared to monotherapy with an alpha-blocker [8].

While the MTOPS study supported the combination of an alpha-blocker and a 5-ARI, the SMART-1 study showed these benefits can be maintained with 5-ARI monotherapy in the majority of men after a defined period of time [9]. In contrast to the MTOPS study, the SMART-1 study indicated that the most common ADEs reported were due to 5-ARIs; and these ADEs accounted for four percent of the discontinuations seen in the initial phase of the study [9].

Several years after the MTOPS and SMART-1 study, the CombAT studies further stratified severity and symptoms of BPH by assessing the effects of mono- versus dual therapy on voiding and storage complications of BPH [10]. The results of the study demonstrated that therapy options may be dependent on prostate volume and, in certain clinical scenarios, dual therapy did not provide better long-term control of storage and voiding LUTS when compared to monotherapy with dutasteride [10]. Results further indicated that 5-ARIs not only improved voiding symptoms but were also as effective as alpha-blockers in controlling storage symptoms [10]. With regards to safety and tolerability, the occurrence of any drug- related ADEs was significantly greater with dual therapy [10]. Both of these findings may create a case for the use of 5-ARI monotherapy.

While the results from all three trials cite combination therapy as providing significant benefit over monotherapy options, the extent of contribution from each drug class may be questioned; the evidence dictates monotherapy with 5-ARIs consistently provides greater improvement in various symptom scores compared to alpha-blocker monotherapy [8-11]. This may be due in part to the direct effect on prostate tissue and disease progression. Several additional studies were conducted that demonstrated no significant difference between groups with regards to improvement in symptom scores and deterioration of existing condition upon the removal of an alpha-blocker from dual therapy

[12-14]. One review even concluded that discontinuation of alpha-blockers should be considered for the frail, elderly, or those with concomitant illness or polypharmacy [12].

Several studies have shown the impact 5-ARIs may have on progression of BPH, yet no reports of alpha- blockers have produced such findings [8-14]. The majority of the therapeutic effects seen from alpha-blockers are related to symptom management, which may not be required once the 5-ARI begins to exert full therapeutic effects. Risks (e.g., dizziness and hypotension) associated with alpha-blockers are highlighted in the MTOPS trial. Nearly 27% of the study population using alpha-blockers discontinued the medication due to ADEs [8]. Not only do these ADEs result in discontinuations, but they may result in non- adherence, causing the persistence of these ADEs. Bird et al. found the risk of alpha-blocker-related hypotension, resulting in hospitalization, was highest during the first eight weeks of therapy and the first eight weeks after reinitiating therapy [15]. Hypotension in these cases is typically benign and fleeting; however, the vasodilatory effects of alpha-blockers have been cited to cause hip fractures due to syncope and falls. In the elderly population, falls and fractures are indicative of increased morbidity and mortality, decreased quality of life, and increased healthcare costs [16]. The risks and benefits of an alpha-blocker in prolonged (>1 year) combination therapy should be weighed for each individual patient.

Evaluating BPH regimens for appropriateness of therapy must occur routinely. The European Union Geriatric Medicine Society supplements this recommendation by stressing the importance of medication reviews annually, or every six months in older, frail individuals [16]. The need for routine review in the geriatric population is further enhanced due to the escalation in rates of polypharmacy [3-12]. An increase in the number of drugs subsequently increases the probability of an adverse drug event secondary to MDIs [4]. The addition of just one medication increases the risk of a potential drug interaction by 12 percent [4]; therefore, deprescribing one medication may reduce this risk by the same factor. Though the patient did not complain of any ADEs at the time of the medication review, the tamsulosin has the potential to be the victim in several drug interactions, resulting in ADEs [4-18]. Pertinent to this patient's medication regimen are the documented reports of pharmacokinetic and pharmacodynamic interactions between bupropion and tamsulosin and between risperidone and tamsulosin (Figure 1) [18]. Both bupropion and risperidone are stronger affinity substrates of CYP2D6, compared to tamsulosin, and will competitively inhibit the metabolism of tamsulosin. Risperidone is also a stronger affinity substrate of CYP3A4 and is known to have hypotensive effects. With both metabolism pathways blocked for tamsulosin, and the potential for additive hypotensive effects, the patient is at an increased risk for experiencing hypotension and falls. Deprescribing the alpha-blocker can reduce the risk of such avoidable ADEs. Additional interventions are warranted in this patient to improve his therapeutic regimen, as significant competitive inhibition is observed between other medications (bupropion and risperidone on CYP2D6; risperidone and finasteride on CYP3A4) that could lead to other significant ADEs.

Conclusion

Alpha-blockers have an important role in the management of BPH and LUTS, especially in the initial months of therapy. However, in a frail patient population with a high prevalence of polypharmacy, the reduction of one medication may provide significant benefit. For patients with BPH, who have tolerated six to twelve months of dual therapy, it may be beneficial to recommend deprescribing the alpha-blocker. Monotherapy with 5-ARIs has been shown to be safe and effective for slowing clinical disease progression, reducing the risk of acute urinary retention and the need for invasive therapy, and improving voiding and storage symptoms. Healthcare providers should continue the practice of assessing medication regimens for appropriateness of therapy and deprescribing inappropriate medication therapy.

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