

A Novel Neurologic
Signal: Restless Legs
Syndrome Associated
With Androgen
Receptor Signaling
Inhibitor Therapy for
Prostate Cancer



To the Editor: Restless legs syndrome (RLS) is a neurologic sensorimotor disorder characterized by an urge to move the limbs that worsens during rest in the evening hours. Although several medications are recognized to precipitate or to exacerbate RLS, androgen receptor signaling inhibitors (ARSIs) have only rarely been implicated.¹ Enzalutamide-associated RLS has been reported previously, but to our knowledge, RLS associated with apalutamide has not previously been described.^{1,2}

We report the case of a man in his late 50s with long-standing history of severe RLS that was well controlled with methadone and rotigotine patch after previous augmentation from oral dopamine agonist therapy and unsuccessful trials of multiple alternative agents. Although the plan was to taper off rotigotine and remain on methadone as monotherapy, the patient deferred because of achievement of symptomatic relief and lack of adverse effects. The RLS symptoms remained quiescent throughout treatment of localized prostate cancer, including radical prostatectomy and radiation therapy. After recurrence with osseous metastases, he initially received abiraterone, which was discontinued because of fatigue. He was then prescribed enzalutamide, and within 2 weeks, marked worsening of RLS with

severe insomnia developed after more than a year of clinical stability. Iron studies, renal function, and thyroid function remained normal. Enzalutamide was discontinued in collaboration with his oncology team, resulting in rapid resolution of symptoms.

Because of ongoing oncologic treatment needs, he was subsequently prescribed apalutamide. Within several weeks, he experienced an identical recurrence of severe RLS despite escalation of methadone and rotigotine and the addition of pramipexole. Symptoms remained refractory until apalutamide was withheld, after which both RLS and insomnia again resolved. A subsequent rechallenge reproduced the same clinical syndrome. Following shared decision-making, the patient elected active surveillance rather than continued ARSI therapy, and his RLS returned to baseline control on his prior regimen.

The temporal relationship, reproducibility with rechallenge, and resolution after discontinuation strongly support an association between ARSI therapy and worsening RLS. Whereas RLS is listed as an uncommon adverse event with enzalutamide and has been described in a small number of case reports, this appears to be the first published report involving apalutamide.^{1,2} Potential mechanisms include central nervous system effects related to γ -aminobutyric acid type A receptor modulation, alterations in androgen-mediated iron homeostasis with downstream effects on dopaminergic signaling, and disruption of mesocorticolimbic dopamine pathways.³⁻⁵ Although apalutamide has lower central nervous system penetration than enzalutamide, this case

suggests that clinically meaningful neurologic adverse effects may still occur in susceptible patients.

As the role of ARSIs continues to expand in prostate cancer management, clinicians should recognize worsening RLS as a potential treatment-related adverse effect, particularly in patients with preexisting disease. Early recognition may prevent unnecessary escalation of RLS-directed therapies and facilitate informed discussions about oncologic treatment options. Additional pharmacovigilance and prospective investigation are warranted to better define the incidence and mechanisms of ARSI-associated RLS.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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