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REVIEW

Fundamental Neurochemistry Review: Copper availability as a potential therapeutic target in progressive supranuclear palsy: Insight from other neurodegenerative diseases

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Abstract

Since the first description of Parkinson's disease (PD) over two centuries ago, the recognition of rare types of atypical parkinsonism has introduced a spectrum of related PD-like diseases. Among these is progressive supranuclear palsy (PSP), a neurodegenerative condition that clinically differentiates through the presence of additional symptoms uncommon in PD. As with PD, the initial symptoms of PSP generally present in the sixth decade of life when the underpinning neurodegeneration is already significantly advanced. The causal trigger of neuronal cell loss in PSP is unknown and treatment options are consequently limited. However, converging lines of evidence from the distinct neurodegenerative conditions of PD and amyotrophic lateral sclerosis (ALS) are beginning to provide insights into potential commonalities in PSP pathology and opportunity for novel therapeutic intervention. These include accumulation of the high abundance cuproenzyme superoxide dismutase 1 (SOD1) in an aberrant copper-deficient state, associated evidence for altered availability of the essential micronutrient copper, and evidence for neuroprotection using compounds that can deliver available copper to the central nervous system. Herein, we discuss the existing evidence for SOD1 pathology and copper imbalance in PSP and speculate that treatments able to provide neuroprotection through manipulation of copper availability could be applicable to the treatment of PSP.

KEYWORDS
amyotrophic lateral sclerosis, copper, neurodegeneration, Parkinson's disease, progressive supranuclear palsy, superoxide dismutase 1

1 | INTRODUCTION

Progressive supranuclear palsy (PSP) is considered to be the second most common parkinsonism after idiopathic Parkinson's disease (PD; Alster et al., 2020). It was described as its own syndrome in 1963 through observation of characteristics uncommon in most PD patients, including unexplainable falls, supranuclear gaze, pseudobulbar palsy, axial rigidity, and mild dementia (Richardson et al., 1963).

Abbreviations: ALS, amyotrophic lateral sclerosis; CNS, central nervous system; PD, Parkinson's disease; PSP, progressive supranuclear palsy; SOD1, superoxide dismutase 1.

However, PSP is still frequently misdiagnosed as PD due to broad overlap in clinical features, making its estimated prevalence of approximately 7.1 per 100 000 (pooled global figure) a likely underrepresentation (Swallow et al., 2022). Clinical symptoms of PSP emerge due to neuronal loss within the basal ganglia, brainstem, and cerebellum, and the continued progression of neuronal loss after diagnosis is rapid. Neuronal loss within the pallido-nigro-luysian axis appears to be an early event in the disease (Zhang et al., 2021) and up to 84% neuron loss in the substantia nigra pars compacta at disease endpoint (Oyanagi et al., 2001) is accompanied by the loss of associated afferent neural circuitry (Ruberg et al., 1985).

Pathological lesions in the PSP-affected brain are found within key neuroanatomical regions with initial histological analyses producing evidence for neurofibrillary tangles, tau pathology and demyelination (Steele et al., 1964). Tau pathology in glial cells and surviving neurons within affected regions of the brain provide cardinal hallmarks of PSP confirmed *post-mortem* (Komori, 1999; Kowalska et al., 2004) and this has motivated the development of several tau-directed therapies for PSP. Disappointing results from clinical assessment of these therapies to date (Coughlin & Litvan, 2022), however, have raised the question of whether alternative and/or additional therapeutic targets may be needed. The challenge herein is that outside of tau pathology the understanding of other molecular mechanisms involved in the propagation and progression of neurodegeneration in PSP is relatively limited. The aetiology of PSP is unknown, with age, environmental factors and common genetic variability in *MAPT*, the gene for tau, providing the only known risk factors (Alquezar et al., 2020; Golbe et al., 1988; Litvan et al., 2016).

Herein, we postulate that information gathered from other neurodegenerative diseases may provide useful new insights into PSP and associated therapy development. Specifically, we consider the relationship between pathological accumulation of the frontline antioxidant superoxide dismutase 1 (SOD1; EC 1.15.1.1), tissue availability of its requisite co-factor copper, and therapeutic agents capable of neuroprotection through copper modulation.

2 | DISRUPTED COPPER AVAILABILITY IN NEURODEGENERATIVE DISEASE INCLUDING PSP

Copper is an essential element due to its requirement in iron homeostasis (Holmberg & Laurell, 1947), diverse cuproenzymes (Buse et al., 1999; Fridovich, 1974; Hevel et al., 1999; Konecny et al., 1999; Stepien et al., 1989), neuronal myelination (Zimmerman et al., 1976), and neurotransmitter biosynthesis (Abudu et al., 1998). The natural distribution of copper within the brain is variable in terms of concentration within specific regions (Ramos et al., 2014) and over the course of development and ageing (Ashraf et al., 2019; Escobar-Khondiker et al., 2007; Fu et al., 2015; Palm et al., 1990; Ramos et al., 2014; Tarohda et al., 2004; Wang et al., 2010). Regional distributions of copper reflect the highly organised cytology of the neuroanatomy with distinct grey and white matter compositions. Grey matter regions enriched with neuronal soma have a higher copper content than neighbouring white matter regions enriched with myelinated axons (Krebs et al., 2014). The neuroanatomical regions that contain high levels of copper are the basal ganglia, locus coeruleus, red nucleus, and the cerebella dentate nucleus (Davies et al., 2013, 2014; Dexter et al., 1991; Krebs et al., 2014; Popescu et al., 2009). Astrocytes play an important role in bringing copper into the CNS via their proximity to neurons and to endothelial cells that line the brain capillaries (Tiffany-Castiglion & Qian, 2001). The sequestration of copper by astrocytes is essential to both regulate the distribution of copper to various other cells in the CNS and to protect the CNS from toxicity caused by copper that is in excess to requirement (Bulcke et al., 2014; Dringen et al., 2013).

The impact of disrupted copper availability on neurological function is seen in diseases where copper levels are altered, with copper overloading the hallmark of Wilson's disease (Lorincz, 2010) and copper deficiency being the hallmark of Menkes disease (Kaler et al., 2008). Wilson's disease is caused by mutations affecting the copper transporter *ATP7B* and is associated with neurological symptoms that include tremors, ataxia, rigidity, dystonia, dysphagia and dysarthria, and these often manifest late in the third decade of life (Lorincz, 2010; Machado et al., 2006). Menkes disease, conversely, is caused by mutations that affect the copper transporter *ATP7A* and prevent systemic copper uptake from the gut and result in decreased copper availability. The neurological consequences of Menkes disease include demyelination and progressive neurodegeneration (Kaler, 2013; Moon et al., 2020), with the overall impact being fatality in children 3 years and under (Kaler et al., 2008). This impact is driven by insufficient supply of copper to mitochondria, where it is required for incorporation into cytochrome c oxidase for the generation of ATP. This disproportionately impacts the brain because of its high metabolic demand (Camandola & Mattson, 2017).

In addition to Menkes and Wilson's diseases which exhibit neurological deficits with established molecular connections to copper availability, changes affecting copper availability are also reported in more common neurodegenerative disease such as Alzheimer's disease, PD and amyotrophic lateral sclerosis (ALS), with changes in copper concentration seen within vulnerable areas of the CNS (Davies et al., 2014; Dexter et al., 1991; Hilton et al., 2020; James et al., 2012; Lovell et al., 1998). Some studies indicate no changes in copper within these diseases (Exley, 2006; Uitti et al., 1989), but variations in detection and preparation methods need to be considered. Specifically, assessing total tissue copper content can potentially mask detection of changes that occur within particular regions of interest, as indicated by the accumulation of copper in Alzheimer's disease within regions with pathological hallmarks of neurofibrillary tangles and amyloid plaques (Lovell et al., 1998; Sayre et al., 2000).

Increased recognition of altered copper availability within the CNS therefore comes with methodologies that move beyond total tissue content and begin to inform on changes that can occur within anatomical regions and biochemical fractions of interest. With this consideration in mind, reports on neurodegenerative disease-associated changes in brain copper already extend to PSP. The first

publication on copper concentrations in the brain tissue from cases of PSP reported total tissue copper content for five anatomical regions of interest (Dexter et al., 1991). All indicated a decrease in total copper content, with the cerebellum reaching a statistically significant change (Table 1). A subsequent study that also assessed total tissue copper content provided results that were overall corroborative (Loeffler et al., 1996), with the caudate nucleus in this study highlighted as the region of interest with a statistically significant decrease (Table 1). Notably, the first study also reported elevated iron levels in regions of the PSP affected brain (Dexter et al., 1991). Decreased copper associated with increased iron is reported in the PD-affected substantia nigra where, importantly, copper-dependent ferroxidase activity required for iron export is decreased (Ayton et al., 2013). A similar association between copper availability affecting iron accumulation may be present in PSP. However, elevated levels of ceruloplasmin protein in PSP (Loeffler et al., 1996, 2001) may appear inconsistent with this possibility. But as an acute phase protein, delineating between ceruloplasmin changes in an inflammatory context from its role as a cuproenzyme responsible for regulating cellular iron requires measurement of its ferroxidase activity. Reports on the copper-dependent ferroxidase activity of ceruloplasmin in the PSP-affected brain do not yet exist.

3 | DISRUPTED COPPER AVAILABILITY PROMOTES SOD1 PATHOLOGY

Renamed in 1969 to reflect its enzymatic activity towards superoxide (McCord & Fridovich, 1969), SOD1 is essential, with genetic deletion resulting in cell death (Bhaskaran et al., 2020; Glasauer et al., 2014). Ubiquitously expressed and predominantly located within the cytoplasm, SOD1 is a highly abundant and stable enzyme in its mature form. The immature form of SOD1 must undergo posttranslational modifications to form a fully active and functional enzyme. This includes dimerisation, metalation, and tertiary folding to form a stable homodimer (Arnesano et al., 2004; Banci et al., 2000; Bonaccorsi di Patti et al., 2002; Furukawa, 2013; Roe et al., 1988). The supply of copper to nascent SOD1 involves the copper chaperone for SOD1 (Culotta et al., 1997; Furukawa et al., 2004; Rothstein et al., 1999) which provides one copper atom to each SOD1 monomer subunit. This facilitates the formation of a disulphide bridge that brings together two monomer subunits (Arnesano et al., 2004). Without copper, SOD1 is less stable under physiological conditions (Kabuta et al., 2006). Moreover, copper-deficient SOD1 monomers provide a precursor to the formation of SOD1 aggregates (Furukawa, 2013) and copper insufficiency causes the protein to misfold in a fashion similar to other amyloidogenic proteins associated with neurodegenerative disease (Furukawa et al., 2008; Wang et al., 2003).

As SOD1 has direct links with ALS (Rosen et al., 1993), its role in this disease context has been extensively researched (Bunton-Stasyshyn et al., 2015; Trist et al., 2021). Mutations within the disulphide bridge and within the copper binding domain of SOD1 can promote the formation of insoluble cytoplasmic aggregates within glia and motor neurons in some cases of ALS (Forsberg et al., 2011) and mouse models of the disease (Kato, 2008). Despite ubiquitous expression of mutant SOD1 in ALS and animal models thereof, accumulation of the protein in an aberrant copper-deficient state is most evident within the CNS (Hilton et al., 2018; Hollander et al., 2000). Moreover, promoting the physiological copper state of mutant SOD1 in vivo through pharmacological and genetic interventions is associated with neuroprotection and improved indications of neuronal function (Hilton et al., 2017; Roberts et al., 2014; Williams et al., 2016; Figure 1). Aggregates of SOD1 in ALS-affected spinal cord contain less copper than the surrounding grey matter that contain no SOD1 pathology (Trist et al., 2022) and, like ubiquitin, the copper chaperone for SOD1 is also a constituent of protein aggregates found in cases of ALS (Kato et al., 1989, 2001).

Notably, mutations in SOD1 are not required for aggregation of the protein in neurodegenerative disease. Disruption of copper handling mechanisms and SOD1 pathology are evident in the disease-affected tissue of sporadic cases of ALS which do not involve mutant SOD1 (Hilton et al., 2020; Shibata et al., 1996; Trist et al., 2022).

TABLE 1 Copper changes detected in various neuroanatomical structures in human PSP.

Sample size	Neuroanatomical region	Change compared to age-matched controls	[References] Detection method
Control = 13, PSP = 11	Cerebral cortex	16%↓	Dexter et al. (1991) ICP-MS
Control = 14, PSP = 11	Caudate nucleus	13%↓	
Control = 13, PSP = 11	Putamen	8%↓	
Control = 8, PSP = 7	Substantia nigra pars compacta	13%↓	
Control = 12, PSP = 7	Cerebellum	26%↓*	
Control = 7, PSP = 11	Caudate nucleus	54%↓*	Loeffler et al. (1996) AA-MS
	Putamen	33%↓	
	Substantia nigra	39%↓	

Note: Direction of change indicated (↓) represents a decrease compared to non-neurological control cases.

Abbreviations: AA-MS, atomic absorption mass spectrometry; ICP-MS, inductively coupled plasma mass spectrometry; PSP, progressive supranuclear palsy.

*Denotes $p < 0.05$ when compared to controls (stated by authors).

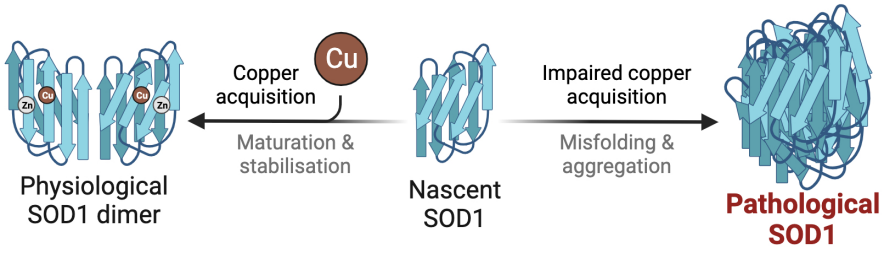

FIGURE 1 Restricted access to copper can cause superoxide dismutase 1 (SOD1) pathology. Under physiological conditions, nascent SOD1 acquires copper via intracellular copper chaperones such as copper chaperone for SOD1 to form a physiologically mature and highly stable homodimer in which each monomer contains one copper atom and one zinc atom. Augmentation of copper-related SOD1 maturation and stability is feasible through genetic and pharmacological interventions. Impaired acquisition of copper by SOD1 can lead to SOD1 pathology, involving SOD1 misfolding and aggregation.

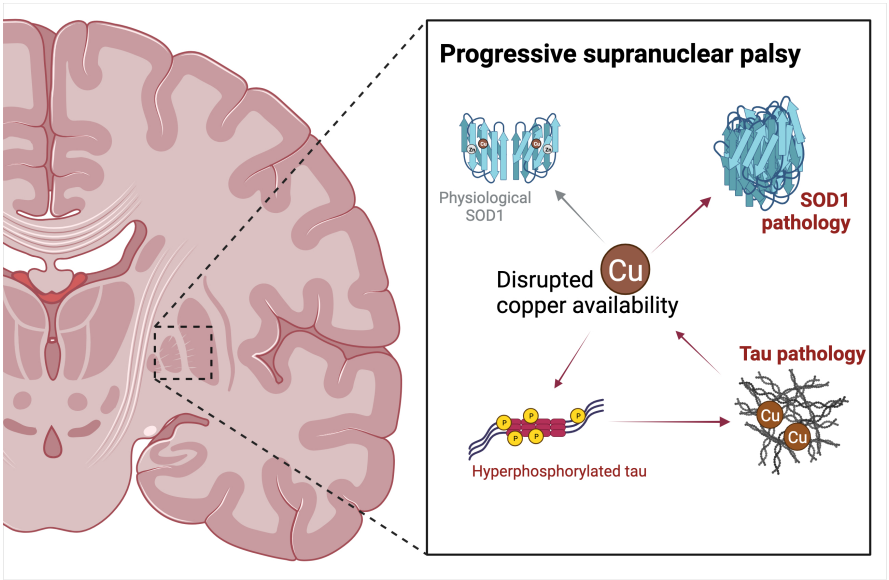

FIGURE 2 Potential involvement of altered copper availability in pathology of progressive supranuclear palsy (PSP). Disrupted copper availability in PSP is implicated through data indicative of altered levels of atomic copper and SOD1 pathology. Aberrant sequestration of copper by aggregated tau may further affect copper availability in PSP and exacerbate formation of pathological features through altered activity of tau kinases and phosphatases such as glycogen synthase kinase 3 and protein phosphatase 2A and impaired maturation of physiologically copper-replete SOD1.

Moreover, data illustrative of decreased copper availability in PD (Ayton et al., 2013) are accompanied by the histological and biochemical data for SOD1 aggregation in the human, PD-affected brain (Nishiyama et al., 1995; Trist et al., 2017). This includes evidence derived from use of conformation specific antibodies raised against epitopes that are naturally inaccessible when buried within the physiological structural fold of SOD1 (e.g., B8H10 and EDI). Immunoreactivity for these antibodies indicates destabilised forms of SOD1 are present in over 70% of substantia nigra pars compacta cells in PD (Trist et al., 2017). Significantly, SOD1 pathology in PD is reported to be a strong correlate of neuronal loss in PD (Trist et al., 2017) even though the cases of PD examined were confirmed free of SOD1 mutations (Trist et al., 2018).

4 | SOD1 PATHOLOGY AS A POTENTIAL INDICATOR OF DISRUPTED COPPER AVAILABILITY IN PSP

Antibodies that specifically detect destabilised forms of SOD1 are yet to be tested on brain tissue from cases of PSP. However, increased immunoreactivity for misfolded SOD1 is detected in cerebrospinal fluid from PSP cases (Tokuda et al., 2019). Reactivity for misfolded SOD1 was less strong in PSP cerebrospinal fluid when compared to cases of ALS (Tokuda et al., 2019). Nonetheless, cerebrospinal fluid from PSP cases was toxic towards neuronal cells grown in culture and this toxicity was remedied through pre-absorption with an antibody to misfolded SOD1 (Tokuda et al., 2019). These data indicate a neurotoxic role for misfolded SOD1 in PSP, but evidence for copper availability contributing to the formation of aberrant SOD1 in PSP cerebrospinal fluid is yet to be produced. Similarly, the only publication to date on SOD1 in PSP-affected brain tissue reported an unquantified increase in SOD1 immunoreactivity in grey and white matter areas with severe tau pathology and neurodegeneration, and highlighted aberrant SOD1 immunoreactivity in glial cells (Cantuti-Castelvetri et al., 2002). The same study also reported increased SOD1 activity in PSP-affected brain regions (Cantuti-Castelvetri et al., 2002) which suggests the accumulation of SOD1 in PSP involves its accumulation in a copper-replete form.

Together, these studies indicate aberrant changes in SOD1 in PSP and highlight that quantitative data are needed to better understand whether SOD1 pathology in PSP involves perturbations

affecting copper availability. A direct assessment of copper in the PSP-affected brain suggests that such perturbations are present (Table 1). But if altered copper availability plays a significant role in PSP, presumably a connection could also be made to tau. Tau pathology, including tau hyperphosphorylation, is the hallmark pathology of PSP (Komori, 1999; Kowalska et al., 2004; Samimi et al., 2021; Wray et al., 2008). Copper binding sites have been identified in tau (Bacchella et al., 2020; Lukács et al., 2019; Ma et al., 2005; Martic et al., 2013) and an interaction between copper and tau promotes tau aggregation (Jing et al., 2021; Zhou et al., 2007). As described above, astrocytes play a major role in copper handling within the CNS and glial tau pathology is a conspicuous feature of PSP (Komori, 1999). Moreover, copper availability can affect tau phosphorylation via the tau kinase glycogen synthase kinase-3β (Hickey et al., 2011; Voss et al., 2014) and the tau phosphatase protein phosphatase 2A (McKenzie-Nickson et al., 2018). Associations between tau hyperphosphorylation, glycogen synthase kinase-3β, and protein phosphatase 2A are reported in PSP (Ferrer et al., 2002; Park et al., 2018). Collectively, these currently disparate lines of investigation indicate a potential relationship between SOD1 pathology and tau pathology in PSP, with disrupted copper availability as a possible unifying feature (Figure 2). Verification of this potential relationship is still needed. If supported, it could provide new opportunity for therapeutic intervention, as discussed below.

5 | IMPLICATIONS FOR THERAPEUTIC INTERVENTION

Therapeutic strategies for neurodegenerative disease based on modulation of biometal availability have been proposed (Barnham & Bush, 2014; Gaeta & Hider, 2005; Zhang et al., 2023), with several translating to clinical trials (NCT03204929, NCT04082832, NCT00471211, NCT03293069, NCT02655315). These include compounds with potential to mitigate tau and SOD1 pathology through modulation of copper availability and, therefore, possible utilisation in the context of PSP. PBT2, for example, is a cell- and blood–brain barrier-permeant copper/zinc chaperone that has been shown to decrease tau pathology and cognitive deficits in tau transgenic mice (Sedjahtera et al., 2018). A mechanism of action for PBT2 involves facilitating the transport of copper and zinc across plasma membranes to elicit a cell signalling response that inhibits tau phosphorylation (Crouch et al., 2011). Corroborative evidence for the mitigation of tau phosphorylation through a mechanism involving copper is derived from studies involving the copper-delivery compound Cu^{II}(gtsm) which increases intracellular levels of available copper (Donnelly et al., 2012) and decreases tau phosphorylation in vitro and in vivo (Crouch et al., 2009; McKenzie-Nickson et al., 2018). Whether the tau response is primarily attributable to the inhibitory phosphorylation of glycogen synthase kinase-3β or the stimulation of protein phosphatase 2A is yet to be resolved (Crouch et al., 2009; McKenzie-Nickson et al., 2018). Nonetheless, improvements in tau phosphorylation after the administration of treatments that modulate available copper support a potential role for copper availability in tau pathology.

Structurally related to Cu^{II}(gtsm), the blood–brain barrier-permeant copper containing compound Cu^{II}(atsm) is neuroprotective in mouse models of ALS and PD (Hilton et al., 2017; Hung et al., 2012; Soon et al., 2011). A protective mechanism of action related to tau pathology has not yet been reported. However, Cu^{II}(atsm) is confirmed to increase levels of physiologically copper-replete SOD1 within the CNS via copper delivery (Roberts et al., 2014; Williams et al., 2016) and the compound targets disease-affected regions of the CNS when administered to patients with neurodegenerative disease (Ikawa et al., 2011, 2015; Okazawa et al., 2022). The neuroprotective activity of Cu^{II}(atsm) has been ascribed in part to regulated release of available copper from the atsm ligand via disease-associated changes in redox conditions and the presence of a pool of apo-cuproproteins (Donnelly et al., 2012; Holland et al., 2009; Yoshii et al., 2012). Collectively, these studies indicate that compounds capable of safely modulating available copper within the CNS have capacity to improve pathological features of neurodegenerative disease that involve tau and SOD1. With tau accumulation being the primary pathological hallmark of PSP and evidence beginning to emerge for the involvement of SOD1 pathology and altered copper availability, it is possible that therapeutic modulation of copper may be a plausible strategy for treating PSP. Direct experimental and analytical verification of this is required.

6 | CONCLUDING REMARKS

There is no effective treatment for PSP. Suspected cases have recourse to treatments that relieve disease-associated symptoms but not the underlying pathology or progression. Cases that present with parkinsonian variant PSP are generally treated with levodopa-carbidopa (to address dopamine deficits) with little benefit. The use of other parkinsonian treatments such as rasagiline (a dopamine breakdown inhibitor; Nuebling et al., 2016) and deep brain stimulation are not recommended for PSP as they do not address significant symptoms such as falls, altered gait, and postural instability (Stamelou & Hoglinger, 2016). More recent therapeutic strategies developed for PSP have been directed towards tau pathology but these have to date not produced positive clinical outcomes. Herein, we have discussed the involvement of SOD1 pathology in PSP and the neurodegenerative conditions of ALS and PD. We have also discussed SOD1 pathology as a potential indicator of disrupted copper availability in PSP and how it may be related to the canonical tau pathology. Verification of a link between SOD1 pathology, tau pathology and disrupted copper availability in PSP could support therapeutic modulation of copper availability as a novel treatment option for PSP.

AUTHOR CONTRIBUTIONS

JLB conceived the idea for this review, conducted the initial literature searches and wrote the first draft. JBWH, JRL, DJH and PJC

conceived the idea for this review and edited the first draft. All authors read and approved the final version.

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CONFLICT OF INTEREST STATEMENT

Collaborative Medicinal Development LLC has licenced intellectual property related to Cu^{II}(atsm) from the University of Melbourne. PJC is an unpaid consultant for Collaborative Medicinal Development LLC. None of the authors has a financial conflict of interest to declare.

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Data sharing is not applicable to this article.

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