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Current treatment of behavioral and cognitive symptoms of Parkinson's disease

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ABSTRACT

Cognitive and behavioral symptoms are common in Parkinson's disease, may occur even in the prodromal stages of the disease, worsen with disease progression, and surpass motor symptoms as the major factors affecting patient quality of life and caregiver burden. The symptoms may be caused by the disease pathology or they may represent adverse effects of treatment, or both etiological factors may contribute. Although many of these symptoms are related to dopaminergic dysfunction or dopaminergic medication, other neurotransmitters are involved as well. Behavioral symptoms including impulse control disorders, apathy, psychosis, as well as mild cognitive impairment and dementia are reviewed with a special focus on current treatment approaches.

1. Introduction

Behavioral and cognitive symptoms are highly prevalent in Parkinson's disease (PD) and their cumulative prevalence increases with the disease progression. The symptoms are distressing both to the patients and their families, have a major impact on patient quality of life, and increase caregiver distress more than the motor symptoms of parkinsonism alone [1–3]. The current available treatment options for cognitive impairment and dementia, psychosis, apathy, and impulse control disorders are, on the whole, less successful in long-term symptom compensation than the treatment options for tremor, rigidity, bradykinesia, and motor fluctuations and dyskinesias. Moreover, the fact that motor, behavioral, and cognitive symptoms coexist in individual patients decreases the otherwise wide range of treatment options for motor symptoms of PD and sometimes leaves the clinician with very few options that are balanced between a good motor state and satisfactory behavioral compensation. Multidisciplinary care, engaging neurologists and particularly movement disorder specialists, psychologists, psychiatrists, functional neurosurgeons, nurse specialists, social workers, and occupational therapists, as well as careful and comprehensive counselling for patients and their caregivers, is needed [4].

2. Impulse control disorders

Impulse Control Disorders (ICD) are failures to resist an impulse, drive, or temptation to perform a typically pleasurable activity that is ultimately harmful to the person or to others because of its excessive nature. These behaviors are both impulsive (lacking forethought or consideration of consequences) and compulsive (repetitious behaviors with a lack of self-control), and they are performed excessively to an extent that interferes in major areas of life functioning [5,6]. ICDs have been conceptualized as "behavioral" addictions, due to extensive overlap with disorders of addiction in terms of risk factors, clinical presentation, cognitive aspects, neurobiology, and treatment [7,8].

The most common ICDs include compulsive gambling, buying, and sexual and eating behaviors. According to the fifth edition of the American Psychiatric Association Diagnostic and Statistical Manual (DSM-V), ICDs are disruptive impulse-control and conduct disorders, including conditions involving problems in the self-control of emotions and behavior. The prevalence varies widely, from 3.5 to 42% [9,10]. Based on the results of a meta-analysis of 14 studies including 2,371 PD patients and 2,168 healthy controls, PD patients had higher ratios for several ICDs than healthy controls, with an odds ratio of 2.07 for having any ICD and of 4.26 for hypersexuality [11]. Studies demonstrated that the risk factors for ICDs are: male sex, younger age, younger age at PD onset, disease duration, more severe non-motor symptoms, impulsive or

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novelty-seeking characteristics, history of smoking, substance abuse, family history of pathological gambling, poorer PD-related quality of life, and being unmarried; genetic susceptibility also plays a role [9,12–16]. ICDs vary in severity, but can lead to devastating consequences, including financial ruin, divorce, loss of employment, and increased health risks [10,17,18]. They are associated with greater functional impairment, decreased quality of life, and increased caregiver burden [17–19]. Imaging studies have shown decreased cortical thickness and dopamine dysfunction (increased dopamine release in ventral striatum, D3 receptor abnormalities) particularly within the reward circuits regions, but also in the dorsolateral prefrontal, orbitofrontal, and posterior parietal cortices that are engaged in top-down control networks [20–23]. The role of serotonin has been debated, and neuropsychological studies have demonstrated reduced cognitive flexibility and planning [24].

2.1. Treatment

In the DOMINION study, which evaluated more than 3000 medicated PD patients [12], ICDs were more common in patients treated with a dopamine agonist (17.1%) than in patients not taking the drug (6.9%). The study also showed that PD patients have an increased risk of having more than one ICD. Prospective cohort studies demonstrated that nearly 40% of patients receiving dopamine agonist therapy with no ICD at baseline developed an ICD over a four-year period [25,26]. The 5-year cumulative incidence of ICDs was 46% [27]; in this study ICDs were associated with DA use and also with the DA dose. Therefore, reducing the dose of the existing dopamine agonist or discontinuing the drug entirely would seem a reasonable option for symptom management. However, many patients do not want or do not tolerate dopamine agonist discontinuation, and dopamine agonist withdrawal syndrome (DAWS) may develop in about 20% of PD patients discontinuing dopamine agonist treatment. DAWS is characterized by anxiety, panic, apathy, social phobia, fatigue, irritability, dysphoria, depression, pain, nausea, vomiting, orthostatic hypotension, drug cravings, and suicidal ideation [28]. Family counselling, actions such as temporarily restricting access to finances, and changes in the medical regimen are necessary. Interestingly, a cross-sectional study of patients using oral dopamine agonist versus transdermal rotigotine found a significant reduction in ICD with rotigotine: almost twice as many patients on oral pramipexole or ropinirole had ICDs as those on transdermal rotigotine patch [29]. Similar results were reported in an observational study of 425 patients with PD [30]. In the same vein, recent longitudinal studies and case studies suggest the beneficial use of continuous dopaminergic pumps such as levodopa continuous intrajejunal infusions or even subcutaneous infusions of apomorphine [31–34] in terms of ICD improvement or complete cessation.

Case reports and small case series studies have described possible effects of neuroleptics, antidepressants, S5αR inhibitor finasteride and various anticonvulsant drugs; however, there is no clear evidence for the use of these drugs in the treatment of ICDs; for review, see Refs. [8,9,15,35,36]. An 8-week, randomized, double-blind, controlled study investigated the opioid antagonist naltrexone in 50 PD patients with ICDs [37], and a 17-week study examined the NMDA antagonist amantadine in 17 PD patients with pathological gambling [38]. Both drugs showed some efficacy. However, the situation with amantadine seems more complex; the DOMINION study [12] demonstrated an increased risk of ICD in the patients taking that drug. More studies with larger sample sizes are warranted. Cognitive behavioral therapy may also be helpful [39].

The relationship between deep brain stimulation (DBS) and ICDs appears complex. There is rather historical anecdotal evidence that ICDs, particularly pathological gambling, may start or worsen after subthalamic nucleus (STN) DBS [40]. Patients receiving DBS may also become more impulsive in their decision making in the ON stimulation condition [41]. However, other studies using STN or GPi DBS demonstrated improvement of ICDs [42–45]. The recently published results of the EARLY STIM study of bilateral STN DBS on non-motor symptoms in PD patients [46] revealed improved hyperdopaminergic behavioral disorders as assessed by the Ardouin Scale subscore [47]. This study recruited 251 PD patients who were disabled by early motor complications, of whom 127 were randomly allocated medical therapy alone and 124 were assigned bilateral STN stimulation plus medical therapy. While the primary outcome was a mean change in quality of life from baseline to two years [48], a secondary analysis evaluated behavioral outcomes [46]. At two years, the Ardouin Scale subscore had decreased with bilateral STN stimulation plus medical therapy (mean change: 1.26 points) while it increased in patients taking medication only (mean change: +1.12 points); the difference was statistically significant ($p < 0{\cdot}0001$). Unfortunately, the study was not powered enough to assess changes in individual ICDs. Likewise, Abbes et al. [49] reported improvement of all ICDs and dopaminergic addictions, apart from eating behavior and hypersexuality, in a long-term follow-up cohort study assessing 69 PD patients with a mean follow-up period of 6 years (3–10 years).

3. Apathy

Apathy is defined as a disorder of motivation that persists over time [50]. The core features include diminished motivation, which must be present for at least four weeks, and reduced goal-directed behavior, goal-directed cognitive activity, and emotions. These symptoms cannot be attributed to diminished levels of consciousness, cognitive impairment, or emotional distress. In addition, there are identifiable functional impairments attributable to the apathy [50–52]. Apathy may coexist with depression, fatigue, cognitive decline, and dementia; however, it may also occur as a distinct syndrome [53].

Apathy is common in PD, affecting 20–40% of patients without dementia; its cumulative prevalence in Parkinson's disease dementia (PDD) may reach up to 60% after 5–10 years [54–57]. Apathy can be present in as much as 20% of drug-naive PD patients [58,59], and it may be an early non-motor symptom of PD [60] and of prodromal PD [61]. Apathy was shown to predict cognitive decline and dementia [62,63] and to increase caregiver burden and distress [3].

Anatomical and metabolic imaging studies reveal abnormalities of the precuneus, the fronto-parietal and orbitofrontal cortices, the insula, and the ventral striatum and mesocorticolimbic pathways, i.e. regions engaged in attention, executive functions, emotions and reward processing, respectively [64]. Functional imaging studies point to limbic dopaminergic denervation as well as noradrenergic and serotonergic lesions [65,66]. Importantly, apathy may occur as a part of dopamine agonist withdrawal syndrome (DAWS); see also the ICD text above. From 63 patients with PD treated with STN stimulation, in whom dopaminergic treatment was decreased by 82% within 2 weeks after surgery, apathy occurred in 34 patients after a mean of 4.7 (3.3–8.2) months and was reversible in half of them at the 12-month follow-up visit [67]. The authors found that the predictors of postoperative apathy (in addition of fast cessation of dopamine agonists) included non-motor fluctuations and high anxiety score at baseline. Importantly, apathy after DBS may be reversible by administration of dopaminergic treatment and D2/D3 acting dopamine agonists in particular [68,69]; see also below.

3.1. Treatment

Treatments for apathy include counselling for families and patients, behavioral strategies to maximize executive functions, and use of medications to treat mood disorders and cognitive disturbances. Psychosocial and behavioral strategies involve providing an individualized daily schedule and structure that help to maintain a satisfactory activity level and enrichment [35,56,70–73]. Studies on the specific treatment of apathy in PD are rather limited; they include trials

evaluating the effects of dopamine agonists, methylphenidate, and cholinesterase inhibitors. Only two small randomized double-blind controlled trials with apathy as the primary outcome have been published, assessing effects of transdermal rivastigmine and oral piribedil; see also below [69,74].

Treatment with some antidepressants, such as SSRIs, was associated with worsening apathy [75]. The authors retrospectively assessed 181 PD patients and studied the association between apathy scale scores and the use of various medications. The use of monoamine oxidase B inhibitors was associated with less apathy. Weintraub et al. [76] demonstrated that atomoxetine did not improve apathy in PD patients with depression and apathy, although apathy assessment was a secondary study outcome.

As for dopamine agonists, Thobois et al. [69] showed in a 12-week double-blind randomized controlled trial that apathy responds to piribedil, i.e. a D2/D3 dopamine receptor agonist. The study was performed in 37 patients with apathy (Starkstein Apathy Scale score > 14) following STN stimulation. Patients received either piribedil, up to 300 mg per day (n = 19), or a placebo (n = 18). At the follow-up visit, the apathy score was reduced by 34.6% on piribedil; it was decreased by 3.2% on placebo ($p = 0.015$). In a randomized controlled study including 122 PD patients, Hauser et al. [77] showed that rotigotine improved the mood/apathy domain score of the Non-Motor Symptom Scale (NMSS), which was the secondary outcome of the study. A post hoc analysis of the RECOVER study also found an improvement in apathy following the use of the rotigotine patch for 4 weeks [78]. Similar results were shown with pramipexole [79]. However, the studies were not designed to include PD patients with apathy. A meta-analysis of 6 randomized controlled trials with rotigotine in a total of 1675 pooled PD patients revealed that the rotigotine transdermal patch significantly improved the mood/apathy domain score of the NMSS [80].

Methylphenidate, a dopaminergic psychostimulant drug (5 mg per day) was found to be beneficial in a case report [81] and in a small group of 7 patients treated with high doses of methylphenidate (1 mg/kg) for 90 days after STN DBS [82]. However, the assessment of apathy was a secondary outcome in that study.

Transdermal cholinesterase inhibitor rivastigmine (9.5 mg/day) was shown to significantly improve apathy after 6 months of treatment in a double-blind, placebo-controlled study of 31 patients with PD and moderate to severe apathy, but without dementia or depression [74].

Based on the results of a recent parallel open-label study (EARLY-STIM) [46], apathy did not significantly change in the two years after STN stimulation surgery. Apathy was measured using the hypodopaminergic subscore of the Ardouin Scale and the Starkstein Apathy Scale [47,68]. Of note, the levodopa-equivalent dose was reduced very slowly and only by 39% in patients who underwent DBS; it was increased by 21% in those who had been assigned pharmacotherapy alone. There was no difference in scale changes between the two groups.

The cohort study that assessed neuropsychiatric symptoms after STN simulation with a mean follow-up duration of 6 years after surgery revealed a worsening of apathy in 25% of patients as compared to 3% before surgery [49]. However, worsening of apathy after this long follow-up period suggests disease progression, rather than direct effects of DBS on the symptom worsening.

4. Psychosis

For a diagnosis of psychosis in PD, at least one of the following symptoms has to be present: illusions, false sense of presence, hallucinations, or delusions. Symptoms are recurrent or continuous for at least one month, and they are not triggered by any psychiatric or general medical condition [83]. They typically occur after the onset of PD [58,61,83,84]; however, a recent prospective cohort study [85] revealed that minor hallucinations (including presence and passage hallucinations and visual illusions) may be present in up to 40% of drug naïve PD patients (as compared to only 5% of age-matched healthy controls), and they may precede motor symptoms of PD by 7–8 months. Psychotic symptoms may be mild or severe; patients may or may not have insight into the pathological nature of the symptoms, and symptoms may be accompanied by affective and other behavioral disturbances. Psychotic symptoms are more common in PD dementia [86]. The prevalence of hallucinations (usually visual images of people or animals) is 20–40%, with the cumulative prevalence reaching up to 85%; the prevalence of delusions is around 5–15%. [87–90]. Risk factors for PD psychosis include higher age, later disease onset, higher PD severity, longer PD duration, hyposmia, depression, diurnal somnolence, REM sleep behavior disorder, visual disorders, severe axial impairment, autonomic dysfunction, visuospatial and attention deficits, and high medical comorbidity and polypharmacy [91–94].

Brain pathology and neurotransmitter changes found to be associated with an increased risk for psychotic symptoms in PD include particularly Lewy bodies in the temporal lobe and cholinergic deficits. Alzheimer's disease pathology may also play a role [91,95]. Functional imaging studies additionally show (particularly ventral) striatal dopaminergic deficits, hypersensitivity of mesocorticolimbic DA receptors [96–99], and increased serotonin-2A (5HT2A) receptor binding within the ventral visual pathway [100]. Reduced engagement of the dorsal attentional network, which exerts top-down control of visual processing, has also been suggested [101].

4.1. Treatment

All antiparkinsonian drugs and even DBS may trigger or worsen psychosis, and several trials of dopamine agonists have shown an increased risk for visual hallucinations compared to placebo [102,103]. On the other hand, continuous delivery of D1/D2 dopamine agonist apomorphine in subcutaneous infusions may even have a potential beneficial effect in the treatment of psychosis [104–108].

The treatment approach involves ruling out medical causes such as delirium, infections, or metabolic disturbance, and removing iatrogenic causes. Anticholinergic medications should be slowly reduced and discontinued, followed by MAO inhibitors and dopamine agonists. If possible, the total levodopa dose (± COMT inhibitors) should also be reduced. Psychoeducative approaches, such as information and guidance about the nature of the phenomena, and cognitive and environmental interventions, such as switching on lights, interacting with the caregiver, concentrating on a hallucinatory object or looking away from the hallucinatory object, and other so-called “coping” strategies should be introduced [109,110].

If these approaches fail, then clozapine (acting as an antagonist of dopamine D2 receptors and serotonin 2A receptors) should be started, since this is the only atypical antipsychotic drug that has clearly demonstrated efficacy for treatment of psychosis in PD [103,111]. However, its use is complicated by the risk of agranulocytosis (although rare, it may occur in 0.38% treated patients), and therefore the need for frequent blood monitoring. Therefore, quetiapine is usually the first antipsychotic drug to begin with, although its use is not evidence-based [103,111,112]. It is advised to titrate the drug very slowly, up to a dose of 100–150 mg/day. If this is not successful, switching to clozapine is recommended [112]. Other antipsychotic drugs, particularly typical neuroleptics, are contraindicated because of motor worsening, cognitive decline, drowsiness and confusion, orthostatic hypotension, urinary incontinence, and falls. A black box warning for increased mortality and cerebrovascular events for elderly patients with dementia-related psychosis has been launched; this is also relevant for PD patients with dementia [113,114].

Pimavanserin, a selective 5-HT2A inverse agonist without dopaminergic, adrenergic, histaminergic, or muscarinic effect was approved by the FDA in 2016 and is shown to be effective and safe in the treatment of PD psychosis [115–117]. A major 6-week randomized double-blind study [116] proved its efficacy in 95 PD patients (mean age 72 years) with psychosis as compared to 90 patients on placebo. The scale for

assessing positive symptoms in PD (SAPS-PD) decreased by 5.79 points in the pimavanserin group as compared to 2.73 points in the placebo group (difference −3.06, 95% CI -4.91 to −1.20; p = 0.001; Cohen's d 0.50). No worsening of parkinsonism was observed. Other study endpoints were also improved, including clinical global impression of change scores, night-time sleep without daytime somnolence, and caregiver burden.

The relationship between visual hallucinations and reduced cortical cholinergic activity suggests that cholinergic agents may improve psychotic symptoms in PD. However, although several case reports, case series, and small open-label trials report some positive effects of cholinesterase inhibitors (and rivastigmine in particular) in reducing visual hallucinations [118–120], there have not yet been well designed randomized double-blind studies. The results of the EXPRESS study [121], which assessed the efficacy of rivastigmine in treating PD dementia in a double blind placebo-controlled trial, revealed that twice as many of the patients without visual hallucinations at baseline developed hallucinations in the placebo group as in the rivastigmine group, suggesting that rivastigmine may protect against the development of visual hallucinations in PD. Patients with PD dementia and visual hallucinations had better effects from rivastigmine than those without visual hallucinations [122]. However, a recently published randomized double-blind study that evaluated the early use of another cholinesterase inhibitor, donepezil (5 mg per day), in 145 non-demented PD patients during a two-year period did not prove any prophylactic effect of the drug on development of psychosis in PD [123]. Significant improvements in visual hallucinations during memantine treatment was reported for DLB but not PDD [124,125].

Electroconvulsive therapy (ECT) has not been studied in controlled trials, but recent case reports and case series suggest improvement in patients with PD and severe psychosis who did not respond to pharmacological treatments [126]. While ECT can improve motor symptoms of PD, it can also cause delirium in cognitively impaired patients [127,128].

5. Cognitive impairment and dementia

Early cognitive deficits predominantly affect attention and executive functions [129] and result particularly from dopamine depletion in the basal ganglia and within the dorsolateral striato-prefrontal circuitry [130,131] as well as in the mesocortical pathways [132]. The cholinergic system has been implicated in cognitive dysfunction and in PD dementia in particular; serotonergic, glutamatergic, and noradrenergic systems could also be involved [132].

MCI in Parkinson's disease has been a heterogeneous clinical entity [133,134] caused by various brain pathologies [132]. It is characterized by cognitive performance decline that is one to two standard deviations (SD) below the mean for an age-matched control population on two or more tests from a neuropsychological battery [135]. Aarsland et al. [136] identified MCI in 18.9% of drug-naïve PD patients; another early PD cohort showed a lower MCI proportion (9%) [58]. According to cross-sectional studies, MCI is present in approximately 25% of all PD patients; attention/executive function deficits seem to be most prevalent [135]. MCI-PD increases the risk of PDD; particularly the posterior cortical dysfunction with impaired semantic language, praxis (figure drawing/copying), and visuospatial deficits is associated with fast conversion into PDD [137,138]. Structural and functional imaging studies support this notion [139–145]. Other clinical risk factors include higher age, family history of PDD, lower education, lower socioeconomic status, disease severity and duration, motor subtype with postural instability and gait difficulty, presence of REM sleep behavioral disorder, changes in speech rhythmicity and prosody, autonomic symptoms, and specific genetic abnormalities (particularly SNCA gene duplication/triplication, glucocerebrosidase gene mutation, H1 tau haplotypes, and APOE4 allelic variants) [146–148]. Biomarkers of cognitive decline in PD have been studied extensively, see e.g. Refs. [149–152].

PDD is characterized by an insidious and progressive cognitive decline that is severe enough to interfere with daily life. Impairment in more than one cognitive domain must be present, and associated behavioral symptoms such as apathy, changes in personality and mood, hallucinations, delusions, and excessive daytime sleepiness may coincide [146]. The mean point prevalence of dementia in PD is between 30 and 40% [153]. The incidence rate increased 5 to 6 times as compared to age-matched healthy controls, and an 8-year cumulative prevalence was as high as 78% [154]. PDD pathology involves wide-spread α-synuclein, but Alzheimer's disease pathology, vascular changes, and other pathologies also play a role [132,155–158].

5.1. Treatment

Before symptomatic treatment is considered, possible contributing factors should be ruled out, including withdrawal of sedating drugs and medication with anticholinergic properties [159], and concomitant physical diseases. Depression and apathy should be considered in the differential diagnosis of early cognitive impairment, although these psychiatric symptoms may accompany PDD.

Studies that specifically examine the effect of dopaminergic treatment on cognition suggest that the effect depends on many variables, including the specific task demands, the PD population tested (de novo versus chronically treated fluctuating patients; presence or absence of cognitive decline/dementia), and genetic factors – with treatment sometimes improving, sometimes having no effect, and sometimes impairing cognition [160].

Symptomatic treatment with acetylcholinesterase inhibitors and memantine has already been extensively reviewed, and recommendations for their use in PDD have been published [103,111]. Recent meta-analyses [161,162] summarize that the efficacy of cholinesterase inhibitors in PDD is evidence-based; particularly rivastigmine and donepezil [121,163] have a positive impact on global assessment, cognitive functions, behavioral disturbances, and activities of daily living. Memantine [124,125] was well tolerated and slightly improved the global impression of change in one study [125]; however, cognitive functions were not apparently enhanced.

Several drugs have been tested in MCI-PD populations in small randomized placebo-controlled studies. Results for rasagiline (n = 151, 24-week trial) [164] and rivastigmine (n = 24, 24-week trial) [165] were negative. One randomized placebo-controlled trial (n = 75, 18-month trial) showed significant effects of creatine (5 g b.i.d.) and coenzyme q10 (100 mg t.i.d.) combination therapy as compared to placebo [166]. After 12 and 18 months of treatment, the differences in the MoCA scores of the combination therapy and control groups were statistically significant. Atomoxetine, an SNRI, (n = 55, 5-week trial) also produced some global positive cognitive effects (a secondary study outcome) in non-demented PD patients; it did not improve depression (a primary study outcome) [76]. Future studies should use specific biomarkers to help to identify distinct PD subgroups that might benefit from potential novel therapies.

As for effects of DBS on cognitive outcomes, a recent meta-analyses of randomized controlled trials [167] showed that STN stimulation, as compared to internal pallidal stimulation (GPi DBS), was associated with subtle declines predominantly in attention, working memory and processing speed, phonemic fluency and learning, and memory; however, there were no significant differences in terms of quality of life. A systematic review and meta-analysis [168] demonstrated decreased performance only in the Stroop color-naming test in the STN DBS vs. GPi DBS. While PD patients with major cognitive impairment are not good candidates for STN DBS surgery [169,170], advanced PD patients with cognitive decline may still be indicated for continuous infusion therapies with levodopa or apomorphine [171,172].

Finally, non-pharmacological interventions may be beneficial in distinct patient subgroups, including exercise, cognitive training, non-

invasive brain stimulation methods, and other techniques to enhance angiogenesis, synaptic plasticity, and neurogenesis [173–178]. This is an exciting and developing field, although it is beyond the scope of this brief review.

In conclusion, cognitive and behavioral symptoms are common in PD, and they have a major impact on patient quality of life and caregiver burden. The behavioral symptoms may represent adverse effects of manipulation of dopaminergic treatment; dementia in PD is particularly caused by cholinergic deficits. Both continuous dopaminergic infusions and DBS surgery may reduce hyperdopaminergic behaviors. While PD patients with MCI may still be considered candidates for dopaminergic pumps, they should not be indicated for STN-DBS surgery. Neuroprotective or disease-modifying drugs for treatment of cognitive impairment in PD are awaited.

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