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Review Article

Functional deficits in attenuated psychosis syndrome and related conditions: Current and future treatment options

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1. Introduction

The schizophrenia spectrum has been a long-time concept and includes conditions that are related genetically and phenomenologically to schizophrenia, such as schizoaffective disorder, schizotypal personality disorder (SPD), and attenuated psychosis syndrome (APS). The spectrum, now officially recognized within Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), also reflects the genetic and neurobiological relationships between schizophrenia, schizoaffective disorder, and SPD (Clark et al., 2017). APS, although not currently recognized as part of the spectrum within DSM-5 (Tsuang et al., 2013), has been shown to predict conversion to full-scale schizophrenia spectrum disorders (Zuschlag et al., 2016), potentially warranting its inclusion. Often referred to by a variety of terms such as the prodrome, at-risk mental state, or ultra-high-risk, APS is characterized by subthreshold levels of psychosis, negative symptoms, and social, productive, and cognitive deficits (Glenthøj et al., 2016; Lam et al., 2018; Piskulic et al., 2012; Tsuang et al., 2013). Importantly, patients diagnosed with APS do not uniformly either convert to psychosis or recover; rather, many of these individuals go on to develop other conditions, which may include SPD.

A central feature of the spectrum, noted since its earliest description, is cognitive impairment; this is seen in schizophrenia and in other conditions of the spectrum including SPD. Impaired cognition is also observed in individuals who eventually develop schizophrenia when they are seen during their premorbid or prodromal periods, and in unaffected first-degree relatives of people with spectrum conditions, including children who are potentially vulnerable (Harvey et al., 1981) and those who have likely already passed the age of highest risk for developing schizophrenia (Keefe et al., 1994).

Impairments in the ability to perform everyday functions are a central feature of schizophrenia and, more recently, have been studied in the spectrum. Since the first descriptions of schizophrenia, the pervasive inability to sustain employment, social relationships, and functional independence has been reported (Harvey et al., 2007). Cognitive impairments are central determinants of these aspects of disability (Green, 1996), and in the last 15 years, it has been proposed that the influence of cognitive deficits on disability is largely mediated by their impact on functional capacity (i.e., the ability to perform critical, cognitively demanding functional skills). These include social and vocational skills, and everyday functions, such as medication management and activities of daily living (Harvey et al., 2007).

Across the spectrum, a number of studies have linked cognitive impairment, functional capacity, and everyday functioning. Recently, attempts have been made to intervene with spectrum members who do not meet the criteria for schizophrenia by using rehabilitation-focused interventions including cognitive remediation. Such efforts are longstanding in schizophrenia (but are a new development in other spectrum conditions), and the results of meta-analyses support their efficacy (McGurk et al., 2007; Wykes et al., 2011). Interestingly, in the context of relatively poor results for pharmacological interventions aimed at cognition in schizophrenia, there have been several successful interventions using pharmacological approaches in SPD (McClure et al., 2007; McClure et al., 2010; Rosell et al., 2015).

This paper reviews cognitive impairments, functional capacity deficits, and impairments in everyday functioning of people in the

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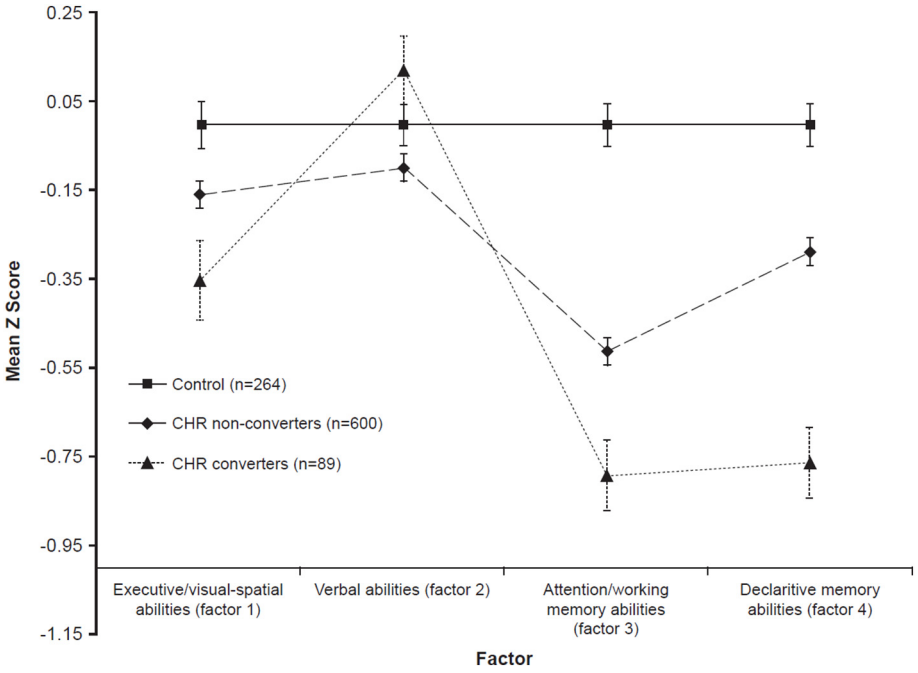

Fig. 1. Cognitive deficits in the NAPLS study.
CHR, clinical high-risk; NAPLS, North American Prodrome Longitudinal Study
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schizophrenia spectrum who do not meet the criteria for schizophrenia, with a focus on characteristics and recent treatment approaches. This will include both cognitive remediation and pharmacological-focused efforts and will address improvements in cognition and functional capacity using these interventions.

1.1. Specific features of attenuated psychosis syndrome

Prodromal features of schizophrenia have been described for many decades and have typically included deterioration in social and functional competence prior to the onset of psychotic symptoms. Furthermore, cognitive functioning appears to change over the lifetime of psychotic symptom development. As noted by Seidman et al. (2016), "there is ample evidence of significant but milder impairments during the premorbid phase, greater deficits during the prodromal or clinical high-risk (CHR) period [of psychosis], culminating in relatively severe deficits in the first episode and chronic phases (Seidman et al., 2016)."

Several large-scale studies have focused on cognition in prodromal cases, including the North American Prodrome Longitudinal Study Phase 1 (NAPLS-1) (Seidman et al., 2010) and 2 (NAPLS-2) (Seidman et al., 2016), the Longitudinal Youth at-Risk Study (LYRIKS) in Singapore (Lam et al., 2018), and several other studies conducted in Europe and Australia (Dickson et al., 2018; McDonald et al., 2018; Mollon et al., 2018; Nelson et al., 2018a; Nelson et al., 2018b). Analyses of data from NAPLS-2 revealed that among 609 patients at CHR, 74 (12%) converted to psychosis, 242 (40%) did not convert, and 293 (48%) went on to develop other outcomes (McLaughlin et al., 2016). As of 2018, 10% of patients in the LYRIKS study were converters; of the 90% who did not convert, 54% were found to remit and the other 46% remained impaired over the entire follow-up period (Lam et al., 2018). Longer-term studies with up to 10 years of follow-up suggest that those who are stably impaired at 2 years do not show marked changes toward conversion to psychosis (Klosterkotter et al., 2001; Nelson et al., 2013) or remission of symptoms (Klosterkotter et al., 2001).

Thus, a substantial proportion of individuals within NAPLS, and other similar studies, are not converted/recovered and may potentially represent the earliest stages of SPD. Indeed, non-remitting patients with APS have been suggested to demonstrate similar cognitive and functional deficits to those observed in SPD populations (Harvey, 2018). In fact, SPD was used as one of the potential entry criteria for adolescent patients (age < 19) enrolled in NAPLS-2, (Seidman et al., 2016), although not all cases met criteria.

From a clinical perspective, APS cases are selected on the basis of the presence of attenuated psychosis, while it is possible to meet criteria for SPD without that level of severity of attenuated psychosis. It has been reported consistently (Cannon et al., 2008; McLaughlin et al., 2016) that the severity of attenuated psychosis at baseline predicts risk for conversion in APS samples, so non-converting non-remitters, cases who meet SPD criteria in the long term, would be expected to manifest lower levels of attenuated psychosis at baseline.

2. Cognitive impairment in APS

Numerous studies have examined the cognitive-impairment profile of APS (Cannon et al., 2008; Lam et al., 2018; McLaughlin et al., 2016; Niendam et al., 2007; Seidman et al., 2010; Seidman et al., 2016). These cognitive deficits have been shown to diminish when patients remit from APS; however, for non-remitters, cognition remains poor and appears to be associated with sustained poor functional outcome (Lam et al., 2018). Interestingly, NAPLS identified that the cognitive deficits present in APS appeared remarkably similar to those seen in first episode psychosis (FEP) (Seidman et al., 2010, Seidman et al., 2016). Cognitive deficits were present on average across the whole NAPLS APS population; however, those who converted to psychosis demonstrated the most substantial levels of cognitive impairment, particularly regarding attention/working memory and declarative memory (Fig. 1) (Seidman et al., 2010, Seidman et al., 2016). Interestingly, marked cognitive impairments were already present at the time of APS detection (baseline) in those patients who converted to psychosis (Harvey, 2018; Lam et al., 2018; Seidman et al., 2010; Seidman et al., 2016). As noted by the NAPLS researchers, there is no evidence of cognitive decline in the longitudinal follow-up study from detection of the prodrome to development of psychosis in cases who convert (Carrión et al., 2018b).

3. Functional capacity in APS

The path to functional disability may begin with cognitive impairment, which then underpins deficits in functional capacity (i.e., the ability to perform real-world functions) (Harvey et al., 2007); however, very few studies have focused on such capabilities. Nevertheless, the Map test, developed by the NAPLS group to assess functional capacity in adolescent and young-adult high-risk populations, has been applied to ~80% (n = 609) of the NAPLS CHR study sample (n = 764) (McLaughlin et al., 2016). The task requires participants to complete a set of errands as part of a fictional shopping trip, emphasizing the ability to process multiple instructions simultaneously, and thus measuring the specific skill-set required to perform a particular real-world function (McLaughlin et al., 2016). Map task performance, and therefore functional capacity, was able to significantly predict conversion to psychosis, independent of intellectual deficits, clinical symptoms, and real-world role achievement (McLaughlin et al., 2016).

4. Real-world functioning in APS

Real-world functioning has emerged as an important predictor of conversion to psychosis based on the results of several studies, all of which produced comparable results. For example, within a population of patients with APS, almost half were identified as experiencing either a poor social (48%) or poor role (49%) outcome, while 33% experienced both outcomes (Carrión et al., 2013). Cognitive predictors were found to be significant in both outcome groups and were similar to those identified in the NAPLS study (Carrión et al., 2013; Seidman et al., 2010). In a recent NAPLS-2 sub-study that looked at everyday functioning and conversion (Carrión et al., 2018a), social functioning (both at baseline and during disease progression) was a more important predictor of conversion than role functioning. Consistent with clinical impressions over the course of decades, deterioration in interpersonal relationships was empirically found to be a strong predictor of development of psychosis (Carrión et al., 2018a).

5. Cognitive impairment in SPD

As discussed earlier, data from the NAPLS sample and others indicate that a substantial proportion of the population does not recover or convert to psychosis; such patients may be representative of the earliest stages of SPD (Harvey, 2018; McLaughlin et al., 2016). Considerable research has been conducted to study cognitive deficits associated with SPD (Rosell et al., 2014; McClure et al., 2013), and stable, non-converting patients with APS are often recruited to such studies. In comparison to healthy controls and patients with personality disorders unrelated to schizophrenia, patients with SPD exhibit cognitive impairments on a variety of measures (Mitropoulou et al., 2005; McClure et al., 2013). Such deficits appear to be specifically associated with working memory, episodic memory, and delayed recall (Fig. 2a). Working memory, measured according to the Paced Auditory Serial Addition Test (PASAT) accounted for the majority of variance between SPD and personality disorders unrelated to schizophrenia groups, and is suggested to represent a core neuropsychological deficit of schizophrenia spectrum disorders that may underlie several of the cognitive deficits observed in SPD. Indeed, removal of the PASAT as a covariate measure was shown to abolish all group differences (Fig. 2b) (Mitropoulou et al., 2005).

Cognitive impairments in APS have been studied somewhat more broadly and have included essentially all of the domains examined in schizophrenia. Some additional research in cognitive neuroscience in APS has also been completed. For instance, a study by Niendam et al. (2013) examined performance of patients with APS on a measure of context processing, the AX-Continuous Performance Test (AX-CPT) and found impairments in both task performance and in brain activation associated with task performance. Similar results were reported in SPD cases, who were found to also manifest specific deficits in context processing on the AX-CPT (McClure et al., 2008) compared with individuals with non-schizophrenia spectrum personality disorders.

6. Functional capacity in SPD

In addition to the cognitive deficits discussed above, a study comparing patients with SPD, avoidant personality disorder (AvPD), and healthy controls, identified real-world functioning and functional-capacity impairments as key features of SPD (McClure et al., 2013). Patients with SPD performed significantly worse on the UCSD Performance-Based Skills Assessment (UPSA; a measure of functional capacity), compared with patients with AvPD and healthy controls (McClure et al., 2013). Furthermore, functional capacity was correlated with cognitive performance in the SPD group (McClure et al., 2013), thus supporting the hypothesis that functional capacity is intrinsically linked to cognitive deficits across the spectrum (Harvey et al., 2011; McClure et al., 2013). Such performance-based assessments of functional capacity may reflect a primary, measurable endophenotype of the schizophrenia spectrum (Harvey et al., 2011, McClure et al., 2013).

7. Real-world functioning in SPD

Despite the prevalence, and cognitive and functional-capacity limitations, of patients with SPD, research on real-world functioning is sparse. In the study mentioned previously, patients with SPD were significantly less likely to be living independently or to have obtained a bachelor's degree compared with the AvPD and healthy groups. Although no significant between-group differences were observed in the proportion of currently employed individuals, those with SPD were found to earn a significantly lower hourly wage than healthy controls (McClure et al., 2013). In a different and larger study, employment functioning in patients with SPD was found to be reduced versus patients with paranoid personality disorder, and patients with SPD generally worked in less cognitively challenging roles requiring minimal social contact (McGurk et al., 2013).

8. Treatment of cognitive impairment

8.1. Pharmacological cognitive enhancement

To date, despite a lack of success with pharmacological interventions for cognitive impairment in schizophrenia, three agents targeting cognitive enhancement in SPD: guanfacine (McClure et al., 2007), pergolide (McClure et al., 2010), and dihydrexidine (DAR-0100A) (Rosell et al., 2015), have shown promising results in double-blind, placebo-controlled trials. Interestingly, all three drugs failed to improve cognition in patients with schizophrenia who were receiving antipsychotic medication, with results published from two of these studies (Friedman et al., 2001; Girgis et al., 2016). Guanfacine, a norepinephrine α_2-agonist that acts post-synaptically in the pre-frontal cortex, was shown to improve cognitive processing versus placebo in patients with SPD (McClure et al., 2007). Using the AX-CPT, the guanfacine group exhibited significantly fewer BX errors and significantly higher AY errors, indicative of an increased normal response bias, compared with baseline measurements in the placebo group (McClure et al., 2007). The dopamine D_1, D_2-agonist, pergolide, has also been assessed for the treatment of cognitive abnormalities in patients with SPD (McClure et al., 2010); pergolide treatment led to statistically significant improvements in verbal learning and memory, verbal working memory, and executive functioning (all hypothesized to be associated with dopamine activity), compared with placebo. Finally, dihydrexidine, a dopamine D_1-agonist, significantly improved PASAT performance among patients with SPD versus placebo in a proof-of-concept study (Rosell et al., 2015). These results converge to suggest the potential for substantial cognitive gains in patients with APS or SPD

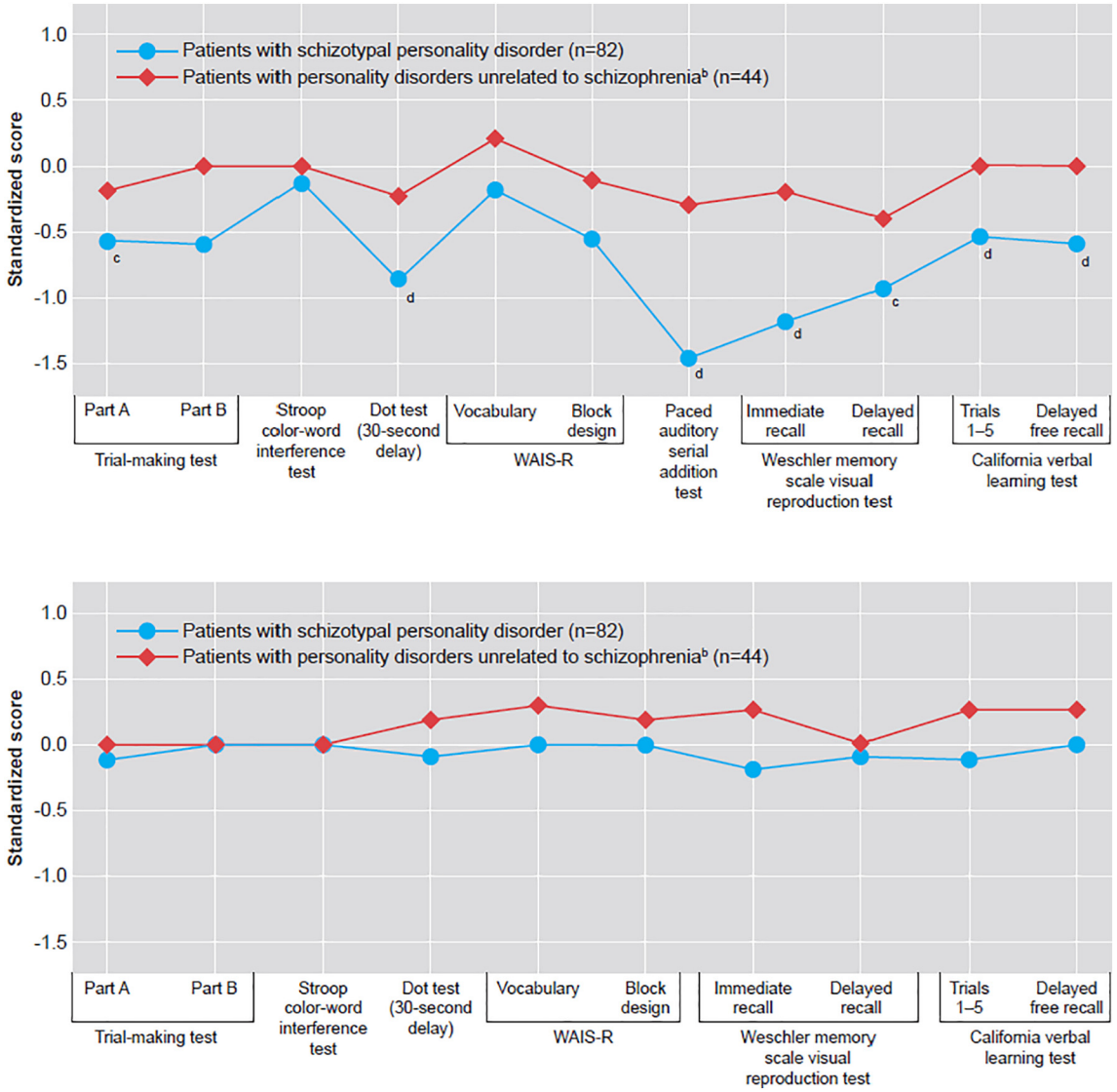

Fig. 2. Neuropsychological performance profiles of personality disorder groups (A); after paced auditory addition test performance controlled (B)[a].
[a]Regression-based approach for normative standards with age, education, gender (A), and Paced Auditory Serial Addition Test score (B) controlled; performance of healthy volunteers (N = 63) has been set to zero (SD = 1). Repeated measures analysis of variance showed an overall significant effect of diagnosis (F = 6.9, df = 2, 186, p < 0.001) (A) and no significant effect of diagnosis (B).
[b]Any personality disorder other than schizotypal, schizoid, or paranoid.
[c]Patients with schizotypal personality disorder significantly differed from healthy volunteers (post hoc analysis).
[d]Patients with schizotypal personality disorder significantly differed from both healthy volunteers and those with personality disorders unrelated to schizophrenia.
WAIS-R, Wechsler Adult Intelligence Scale–Revised; SD, standard deviation.

by using pharmacological interventions.

8.2. Computerized cognitive training

Computerized cognitive training (CCT) is commonly used in the treatment of psychosis and appears to have benefits when targeted at patients with APS and FEP. Indeed, a pilot study assessing the effect of CCT on cognition (40 h for 8 weeks) revealed significant improvements in processing speed in a pre-to-post CCT CHR population (Hooker et al., 2014). Trends toward improvements in visual learning, visual memory, and global cognition were also apparent following CCT. The study also suggested that 20–25 h of CCT may be sufficient for cognitive benefit, with only minimal improvements seen thereafter. A subsequent randomized controlled trial comparing CCT (40 h for 8 weeks) with a standardized computer game control revealed verbal memory to be significantly improved following CCT in a CHR population (Loewy et al., 2016a). Additionally, CCT (up to 40 h) induced significant gains in global cognition, verbal memory, and problem-solving in patients with recent-onset schizophrenia, versus a computer game control group (Fisher et al., 2014).

There has been remarkably little research targeted at CCT in SPD. A recent study attempted a strategy of augmentation of cognitive remediation therapy in SPD using guanfacine in combination with CCT, with 50% of patients randomized to a therapeutic dose of guanfacine, while the other half received placebo. Outcomes were examined using the Measurements and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) and UPSA. Combined therapy led to significant improvements in reasoning and problem-solving, and UPSA total score, compared with CCT plus placebo (McClure et al., 2019). Additionally, CCT was associated, across guanfacine treatment status, with improvements in speed of processing, verbal learning, and visual learning (McClure et al., 2019).

The effect sizes for these improvements were considerably larger than the expected effect sizes seen with retesting and practice alone on the MCCB (Keefe et al., 2017).

9. Conclusions

Significant cognitive impairment appears to be present at the point of APS detection in most cases (Harvey, 2018; Lam et al., 2018; Seidman et al., 2010; Seidman et al., 2016), and cognitive impairment does not progress with, or occur as a result of, the development of psychosis. Importantly, patients who demonstrate the most-elevated levels of cognitive impairment at the time of detection, along with clinical symptoms of APS, are at the highest risk of conversion to psychosis (Harvey, 2018, Lam et al., 2018, Seidman et al., 2010, Seidman et al., 2016). Although few studies have focused on the role of functional capacity, these abilities are of primary importance for functional and social achievement in the real-world and therefore, may constitute a new marker of impending illness. Indeed, the Map task was shown to be predictive of conversion to psychosis, independent of intellectual deficits, clinical symptoms, and role achievement (McLaughlin et al., 2016). Overall, based upon the NAPLS sample, cognitive impairment, inability to perform functional-capacity tasks, and disability in everyday functioning are suggested to aggregate in patients with APS who tend to convert to psychosis (McLaughlin et al., 2016; Seidman et al., 2010; Seidman et al., 2016). Thus, NAPLS has revealed a number of indicators, present at the point of APS detection, which may help to predict the course of illness for such patients.

Similar cognitive and functional deficits are apparent in both APS and SPD populations (Harvey, 2018), leading to the hypothesis that patients with APS who do not convert or recover may be representative of those in the earliest stages of SPD. Furthermore, as with APS, cognitive impairment, everyday disability, and functional-capacity impairment are present in patients with SPD (Harvey et al., 2011; McClure et al., 2013; McGurk et al., 2013; Mitropoulou et al., 2005; Rosell et al., 2014), with a similar impairment signature to that of schizophrenia. In particular, working memory is suggested to be of primary importance in the cognitive deficits observed in SPD populations (Mitropoulou et al., 2005), and there is a large discrepancy in terms of performance outcome in patients with SPD versus those with other personality disorders (Mitropoulou et al., 2005).

Despite a lack of success in schizophrenia, a number of pharmacological interventions have now been assessed for the treatment of SPD with promising results (McGurk et al., 2007; McClure et al., 2010; Rosell et al., 2015). CCT has also demonstrated efficacy in APS, SPD, and FEP, suggesting potential for this route of therapy (Fisher et al., 2014; Hooker et al., 2014; Loewy et al., 2016b). Recently, the use of combined therapy (CCT plus pharmacological intervention i.e., guanfacine) has demonstrated some incremental benefit in the treatment of SPD (McClure et al., 2019).

Overall, cognitive impairment and functional capacity are proposed as important characteristics of both APS and SPD. Several studies suggest that it may be possible to induce cognitive improvement using pharmacological interventions, CCT, or some combination of the two, in patients who are not yet receiving antipsychotics. The primary goal of treatment is disability reduction, because increasing disability predicts conversion, and because SPD is stable and persistent over the individual's lifespan, leading to long-term morbidity even in the absence of psychotic symptoms.

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