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Turning the Spotlight on Apathy: Identification and Treatment in Schizophrenia Spectrum Disorders

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Among negative symptoms, apathy is central to the impairments in real-life functioning in schizophrenia spectrum disorders (SSD). Thus, optimizing treatment for apathy appears key to improve outcomes. In treatment research, however, negative symptoms are typically studied as a unifactorial construct. We, therefore, aim to shed necessary light on the status of apathy identification and treatment in SSD.

Key words: Avolition/experiential symptoms/negative symptoms/psychosis/biological treatment/psychosocial treatment

Introduction

Primary negative symptoms are core phenomena in schizophrenia spectrum disorders (SSD) negatively affecting psychosocial functioning throughout the course of illness.[1] Current consensus definitions depict 5 negative symptoms clustering into 2 domains with partly separate underlying mechanisms.[2] The expressive domain comprises blunted affect and alogia, whereas the experiential domain comprises avolition-apathy, anhedonia, and asociality.[1] Importantly, negative symptoms occurring secondary to depression, medication side effects, substance use, environmental deprivation, or positive psychotic symptoms are prevalent in SSD.[3] They are a challenge to the identification of primary negative symptoms and may respond to treatment of the underlying cause.[3]

Apathy is defined as a reduction of motivation and the initiation and persistence of goal-directed behavior,[4] where the accompanying emotions (enthusiasm) and thoughts (interest, desire) may also be affected.[4] Apathy is associated with a poor quality of life[5] and with adverse effects on real-life functioning across illness phases,[5–7] surpassing impairments caused by other negative symptoms.[8] Moreover, apathy is proposed as central to the development and continuation of other negative symptoms, suggesting that these may also improve if apathy is treated.[8] A meta-analysis reported an apathy point prevalence of 50% in high-risk populations, 28% in first-episode psychosis (FEP), and 73% in multiple-episode psychosis.[9] Longitudinal prospective studies in FEP patients found that up to 50% experience clinically significant apathy[7] and 30%–40% remain apathetic 10 years later.[5,10] Recent evidence suggests that a delay in first treatment is a risk factor for apathy both early and later in the course of illness.[7,10,11]

Albeit unique pathways underlying the development of apathy have been suggested,[8] the basis for the development of apathy partly overlaps with the basis of other experiential symptoms.[1,2] Relevant mechanisms may include aberrant motivation and reward processes, cognitive impairment, demotivating beliefs, disturbances of selfhood and self-agency, and diminished trait-level optimism causing low expectations of positive outcomes.[2,12]

Notably, the treatment options are limited, leaving apathy a key target for treatment research.[8] This is, however, rarely reflected in clinical trials, where negative symptoms typically are studied as a unifactorial construct.[13] We here aim to give an update on the status of identifying and treating apathy in SSD. To find relevant English language articles for this narrative review on apathy treatment in SSD, we searched MEDLINE (Ovid) and PsycINFO (May 2, 2022) for randomized controlled trials (RCTs)

and systematic reviews using combinations of keywords describing the population (schizophrenia, schizoaffective, and psychosis); intervention (biological- and psychosocial interventions plus examples thereof); comparison group (placebo, active control), and outcomes (apathy, anhedonia, avolition, amotivation, deficit, experiential, and negative symptom).

Identification

Terminology

Apathy is a transdiagnostic phenomenon occurring in neurological disorders such as Alzheimer's disease[14] and in mental illnesses outside of SSD.[15] Although the phenotype has clear face validity, its identification is difficult. The operationalization of apathy has changed over time, differs across neurology and psychiatry,[15,16] and different synonyms are used interchangeably. Whereas "apathy" is commonly used in neurology, "amotivation," "demotivation," "avolition," "avolition-apathy," and "abulia" are also used in psychiatry. The terms "avolition" and "apathy" have been used to describe both a single negative symptom[10,17] and as an alternative label for the experiential domain.[1,2] In the following, apathy is conceptualized as the individual avolition symptom. However, few treatment trials report effects on apathy per se. We have therefore included research on the experiential domain, where treatment effects on apathy are embedded. The terms "apathy" and "experiential domain" will be applied accordingly.

Assessment

The most widely applied negative symptom assessments in psychiatry are observer-rated first-generation scales such as the Scale for the Assessment of Negative Symptoms (SANS)[18] and the Positive and Negative Syndrome Scale (PANSS).[19] The scales focus on observable behaviors and do not evaluate emotions and thoughts. Furthermore, their original negative symptoms subscales comprise some items that are now considered cognitive and disorganized symptoms.[4] Factor analyses have, however, identified factors corresponding to the experiential and expressive domains both in FEP and longer-term psychotic disorders,[17,20] with minimal item variation between cultures.[21]

Specific scales for apathy assessment include the observer-rated Apathy Evaluation Scale, one of the most robust scales for cross-disorder use.[22] The observer-rated second-generation scales, such as the Clinical Assessment Interview for Negative Symptoms[23] and the Brief Negative Symptom Scale,[24] concur with the current consensus on symptom and domain structure and include items assessing apathy. Both scales assess observable and subjectively experienced aspects of apathy and other experiential symptoms.

A point of discussion is whether self-report measures of apathy are valid and reliable. While older studies suggested that they were not,[25] later studies indicate that self- and observer ratings do not differ substantially[26] but tap into slightly different aspects of apathy. The Self-Evaluation of Negative Symptoms[27] includes items reflecting apathy and demonstrates a 5-factor structure corresponding to the consensus for negative symptoms,[27] whereas the Motivation and Pleasure Scale-Self-Report[28] assesses the experiential domain. Both are time-efficient in clinical practice. In toto, using specific scales or second-generation negative symptom scales to assess apathy is recommended.[4] Several of these scales could also be used to assess apathy outside of SSD, such as bipolar- and major depressive disorders.[15] For further detail about assessment, we recommend review articles by Lincoln et al[29] and the European Psychiatric Association.[4]

The secondary sources of apathy are rarely recognized. However, identifying and assessing potential secondary sources is crucial to minimize confounding in clinical trials,[4] where a reduction in, eg, depressive symptoms, may falsely be interpreted as a treatment effect on primary apathy.

Treatment

Current Evidence

The evidence base for treating apathy in SSD is limited because systematic reviews and meta-analyses typically include RCTs reporting negative symptoms as the global score of unifactorial negative symptoms assessed with the SANS or the PANSS.[30] Negative symptoms are also rarely the primary treatment target. In the following, we will refer to RCTs and systematic reviews investigating the treatment of apathy or the experiential domain.

Psychosocial Treatments

Cognitive Behavioral Therapy. Cognitive behavioral therapy for negative symptoms (CBTn) aims to modify demotivating beliefs and encourage behavioral activation. An RCT exploring CBTn efficacy for apathy outpatients reported a reduction in apathy after CBTn plus standard treatment (ST) compared to ST alone.[31] The effect was maintained 6 months post-treatment.[32] Results may have been biased by non-blinding of treatment allocation and more treatment time in the CBTn group. Another RCT from the positive emotions program for schizophrenia found that participants receiving positive emotions program for schizophrenia plus treatment as usual (TAU) showed a significant reduction in the experiential domain compared to TAU at program end and 6 months post-treatment, but a reduction of apathy at 6 months only. After removing participants where treatment allocation was revealed by mistake, the effect on apathy at 6 months was no longer significant.[33] A small, yet methodologically

rigorous meta-analysis of RCTs applying a minimum level of negative symptoms for study inclusion, found a small reduction in experiential domain symptoms after CBT, but not cognitive remediation therapy, compared to TAU.[34]

Social Skills Training. Social skills training (SST) aims to improve social performance, social interaction, or interpersonal skills to minimize the risk of social rejection and withdrawal. One RCT compared nine months of cognitive behavioral social skills training (CBSST) with an active control condition and found a moderate effect size improvement in the experiential domain in favor of CBSST.[35] The relative efficacy of the SST and CBT components is unknown, limiting interpretation.

Cognitive Remediation Therapy. Cognitive remediation therapy (CRT) could address cognitive impairments interfering with motivation and reward processes and mitigate demotivating beliefs. One RCT found a moderate decrease in the experiential domain after CRT plus antipsychotic medication (AP) compared to standard treatment plus AP. Still, the authors regarded findings as preliminary due to the small sample size.[36] Twelve months post-treatment, another RCT reported a significant decline in the experiential domain and apathy specifically after CRT plus AP, compared to healthy behaviors training plus AP.[37] A small pilot study compared a new social cognition remediation intervention (SoCIAL) with a CRT previously validated for functional and cognitive outcomes and found a reduction in the experiential domain only after the SoCIAL intervention.[38] Finally, one study combined individual data from 4 RCTs and reported a reduction in the experiential domain approaching the level of statistical significance for CRT compared to a control condition. However, the effect was not retained at follow-up.[39]

Early Intervention Services. Early intervention services (EIS) provide specialized, low-threshold and multidisciplinary services combining assertive psychosocial treatments, including family psychoeducation and CBT with biological treatment. Studies experimentally reducing the duration of untreated psychosis find early and sustained reductions in unifactorial negative symptoms in intervention- compared to control regions.[50,51] One RCT investigated EIS effects on the experiential domain in FEP participants that after 2 years of EIS were randomized to another EIS-year or standard care. Post-treatment, the experiential domain score was significantly lower in the EIS group.[52]

Biological Treatments

Antipsychotic Medication. Although several meta-analyses concluded with minor beneficial effects on unifactorial negative symptoms for second- but not first-generation antipsychotics compared to placebo,[40,41] no studies reported on apathy as an outcome measure. However, newer agents that do not directly affect dopamine receptors or have an affinity for D_3 receptors may be relevant, eg, cariprazine, roluperidone, and pimavanserin.[42] Compared to placebo, one phase 2b RCT[43] reported that roluperidone, which primarily targets $5HT_{2A}$ and $sigma_2$ receptors, significantly reduced experiential domain symptoms, whereas another roluperidone RCT found a nominally significant reduction in the experiential domain.[44]

Adjunctive Medication. Several drugs have been tested as adjunctive medication to AP.[30] Two RCTs, one severely underpowered,[45] compared the monoamine oxidase B inhibitor rasagiline[46] and the selective serotonin reuptake inhibitor citalopram[45] to placebo and found a significant reduction in apathy and the experiential domain, respectively. The effects of pro-dopaminergic drugs, antibiotics, anti-inflammatory agents, or drugs affecting glutamate neurotransmission or oxytocin pathways on apathy, or the experiential domain have not yet been investigated.

Transcranial Stimulation. Repetitive transcranial magnetic stimulation (rTMS) is one type of noninvasive stimulation of specific prefrontal cortical regions by magnetic pulses. One well-powered, double-blind, sham-controlled RCT, including participants with predominantly negative symptoms, reported a significant reduction in apathy after rTMS compared to placebo,[47] whereas another RCT reported no beneficial effect on the experiential domain.[48] Compared to sham, a double-blind RCT found a large experiential domain reduction after bilateral transcranial direct current stimulation. However, a minimum negative symptom level for inclusion was not applied, and secondary negative symptoms were not controlled for.[49]

Conclusion

The clinician-rated second-generation negative symptom scales or specific apathy scales are the current gold standard for assessing apathy in SSD. These scales assess emotions and thoughts as well as behavior and are more relevant for identification of experiential symptoms. Self-reports may further elaborate on subjective experience. Because assessment scales do not differentiate clearly between primary and secondary sources of apathy, potential secondary sources should be assessed routinely. The evidence base for the treatment of apathy and the experiential domain is limited. There is preliminary support for a beneficial effect of CBTn, SST and CRT, transcranial stimulation, and for roluperidone and adjuvant AD. There are further some indications that EIS enhances positive outcomes.

Future Directions

Improving the assessment of primary- and secondary apathy and running treatment studies targeting apathy with requirements of higher levels for study inclusion appear as logical first steps. A scale integrating the assessment of primary- and secondary apathy could be a valuable supplement. Reanalyzing existing treatment data using item structures reflecting the negative symptom domains could help discover differential treatment effects.[13] Whereas results for adjunctive medication, mind-body psychotherapies, aerobic physical exercise, and music therapy on unifactorial negative symptoms are weak,[30] the effects on apathy could be researched more thoroughly. Adding to conventional research approaches, ecological momentary assessment using actigraphy or smartphone registrations may identify fine-grained individual response profiles.[53] In treatment, transcranial stimulation of the cerebellum may be in the pipeline.[54] Moreover, using virtual reality to simulate real-world goal-directed behaviors,[55] or smartphone-based ecological momentary interventions designed to increase reward sensitivity and motivation could potentially augment treatment effects.[56] It is imperative that future clinical and research efforts target apathy and its detrimental consequences.

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