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FOCUSING ON APATHY: IDENTIFICATION AND MANAGEMENT OF SCHIZOPHRENIA (PSYCHIATRIC DISEASES) SPECTRUM DISORDERS

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Abstract

Apathy has attracted a lot of research interest in the last 10 to 15 years, and physicians who treat populations with neuropsychiatric disorders are beginning to recognize it more and more or more frequently. Apathy is linked to several unpleasant outcomes or negative symptoms, appears to be common in many brain disorders, and may be curable. Apathy is a key component of the negative symptoms of schizophrenia spectrum disorders, and it has a significant impact on how well people function in daily life. (Schizophrenia is a disabling psychiatric disease or a disorder characterized by disturbances in thought, feeling, emotion, and interpersonal and vocational functioning). As a result, optimizing treatment for apathy looks essential to improving results or outcomes. Even though it has therapeutic importance, apathy is generally ignored in treatment and clinical studies; in contrast, adverse outcomes are typically explored as a unifactorial construct. Consequently, our goal is to bring increased attention to the condition of apathy diagnosis and treatment in schizophrenia spectrum disorder. We begin by defining apathy and discussing its prevalence, clinical characteristics, and effects on functioning. Then, we review the diagnostic criteria for apathy in brain disorder, and methods for assessing apathy, including Clinical rating scales, and behavioral measures. Finally, we discuss the available evidence for the treatment of apathy in schizophrenia spectrum disorders, including pharmacological and non-pharmacological interventions or therapies and treatments. The available research data suggests that apathy is a heterogeneous construct that can be caused by a variety of elements, such as neurocognitive deficits, medication side effects, and environmental stressors. As a result, there is no single treatment that is effective for everyone who suffers from apathy. However, there is some data or evidence that suggests cognitive-behavioral therapy, behavioral activation, social skill training, cognitive remediation therapy, early intervention services, and motivational interviewing may be useful in lowering apathy and enhancing functioning. The purpose of the study is to enhance the understanding or awareness of apathy as an important clinical and research issue, which means that everyone should "care" about apathy.

Keywords: Apathy, Schizophrenia Spectrum Disorders, Clinical Rating Scales, Schizophrenia, Pharmacological İnterventions, Non-Pharmacological İnterventions, Cognitive-Behavioral Therapy.

INTRODUCTION

In schizophrenia spectrum disorders (SSDs), primary negative symptoms or apathy are key phenomena that have a detrimental impact on psychological and social functioning across the course of the disorder [1]. The most recent consensus classifications reveal five negative symptoms (Fig. 2) are grouped into two domains with partially distinct from one another shown in (Fig. 1) [2]. Blunted affect and alogia belong to the expressive domain (Diminished Expression), whereas avolition, anhedonia, and sociality belong to the experiencing domain (Avolition/ Apathy) (Fig.

1) [1]. Importantly, SSDs frequently exhibit negative symptoms (Fig. 2) that develop as a result of depression, adverse medication reactions, substance abuse, and environmental challenges [3]. They are challenging to identify as primary negative symptoms or unpleasant outcomes and can react or respond to the therapy for the root cause [3].

Apathy is characterized by a lack of drive or motivation as well as a drop in ambition and the initiation and continuation of goal-oriented actions or activities [4], in which the associated feelings (intense emotion compelling action) and ideas (strong desire, attentiveness) could also be impacted [4]. Apathy is linked to a low standard or quality of living [5] and with unfavorable consequences working in the real world across disease stages; [5-7] worsens limitations brought on by other adverse outcomes or negative symptoms [8]. The development and maintenance of other harmful or negative symptoms are also considered to be fundamentally influenced by apathy, suggesting that treating apathy may also help these symptoms [8]. A meta-analysis found that, in high-risk populations, the apathy point prevalence was reported to be 50%, in multiple-episode psychosis to be 73%, and in first-episode psychosis (FEP) to be 28% [9]. Up to 50% of first-episode psychosis (FEP) patients show clinically significant apathy, according to longitudinal prospective studies, and 30%–40% of these patients are still apathetic ten years later [5,10].

Recent research studies indicate that delaying the initiation of treatment increases the risk of developing apathy during the early stages and later throughout the life span of the disease [7, 10, and 11]. Although distinct processes or mechanisms underlying the onset of apathy have been proposed, [8] the cause for this symptom's emergence shares certain similarities with the other experience symptoms depicted in (Fig. 4) [1,2]. Appropriate mechanisms could include abnormal motivational and rewarding systems, cognitive dysfunction, demotivating behaviors, conflicts of individuality and effortlessness, and reduced trait-level (characteristics) optimism, leading to the low presumption of positive results [2,12]. Notably, limited options for therapy have made apathy the main topic of treatment studies [8]. Clinical studies, however, virtually never support this since unpleasant outcomes or symptoms are frequently studied as a unifactorial system or unbiased construct [13].

In this article, we hope to give you a current assessment of how to recognize, diagnose, and treat apathy in schizophrenia spectrum disorders (SSDs). We looked for randomized controlled trials (RCTs) and systematic reviews of English-language literature that were relevant to this narrative review on apathy therapy or treatment and management in SSDs in the databases MEDLINE and PsycINFO. In our study, we used a combination of keywords to describe the population (schizophrenia, schizophrenia spectrum disorders, and psychosis), the intervention (pharmacological and non-pharmacological interventions or therapies), the comparative group (active control and placebo), and the resultant outcomes or characteristics (apathy, avolition, anhedonia, deficit, asociality, experiential, and unpleasant outcome or adverse symptom).

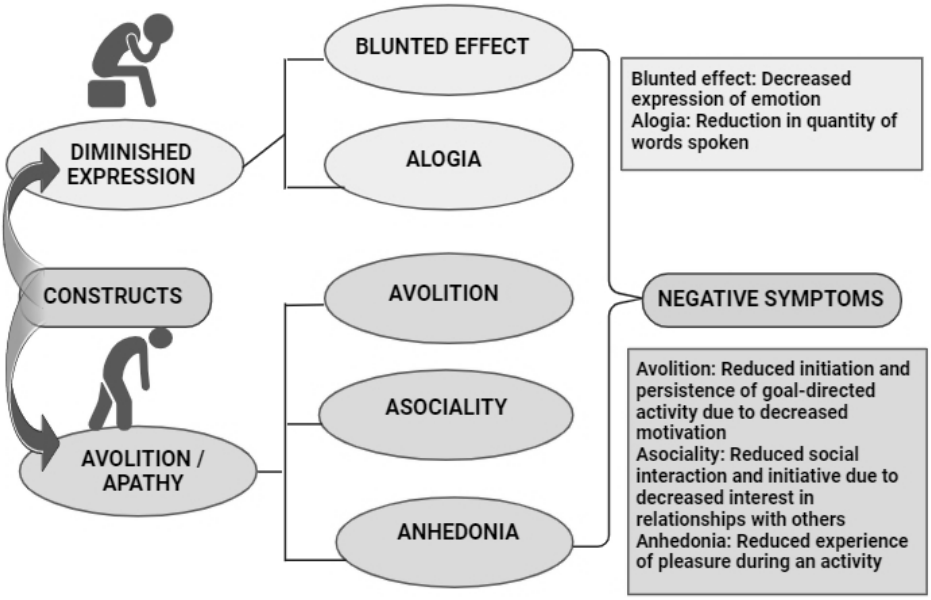

Fig 1: Key Negative Symptom Constructs [57]

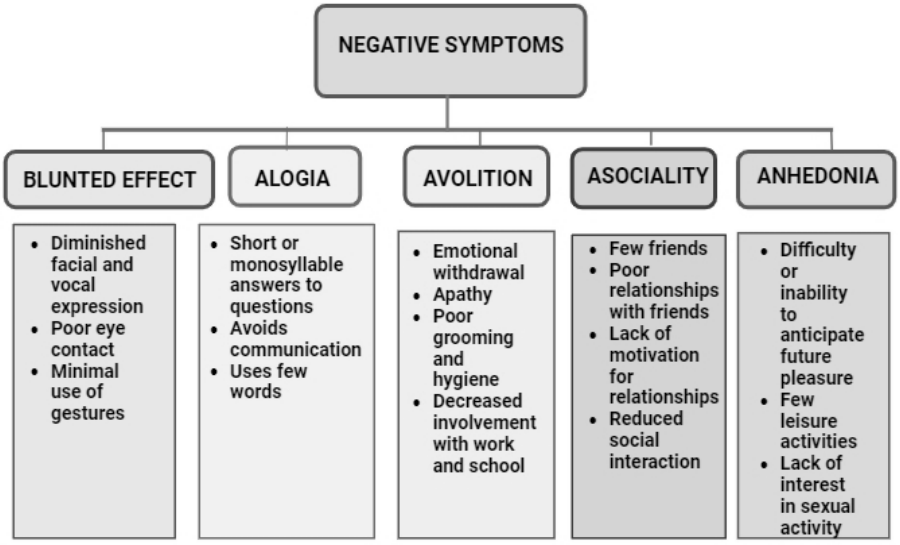

Fig 2: Clinical Presentation of Negative Symptoms [58]

RECOGNITION

Terminology

Apathy is a transdiagnostic condition that can occur in conditions other than schizophrenia spectrum disorder (Fig. 3), such as neurological diseases like Alzheimer's, dementia [14], and other mental or brain diseases [15]. Despite the clear-face validity of the phenotype, it can be challenging to spot (Fig. 3). A variety of differences exist between neurology (nerve system) and psychiatry (mind healing), [15,16] and as the operationalization of apathy has evolved; many synonyms are frequently employed interchangeably. Enthusiasm, demoralization, avolition, and avolition-apathy are also used in psychiatry despite apathy's widespread use in neurology. The words "avolition" and "apathy" have both been used to refer to a single unpleasant outcome or symptom. [10,17] and a new designation for the experimental

or research sector [1,2]. Apathy is viewed as a specific avolition symptom in the sentences that follow. Few therapy trials, nevertheless, have examined the effects of apathy in isolation. To better understand how treatments affect apathy in the experiential domain, we have incorporated research in this section. The terms experiential domain and apathy shall be used appropriately. (Fig. 4) illustrates the Symptoms and neuroanatomical substrates of apathy, depression, and alexithymia.

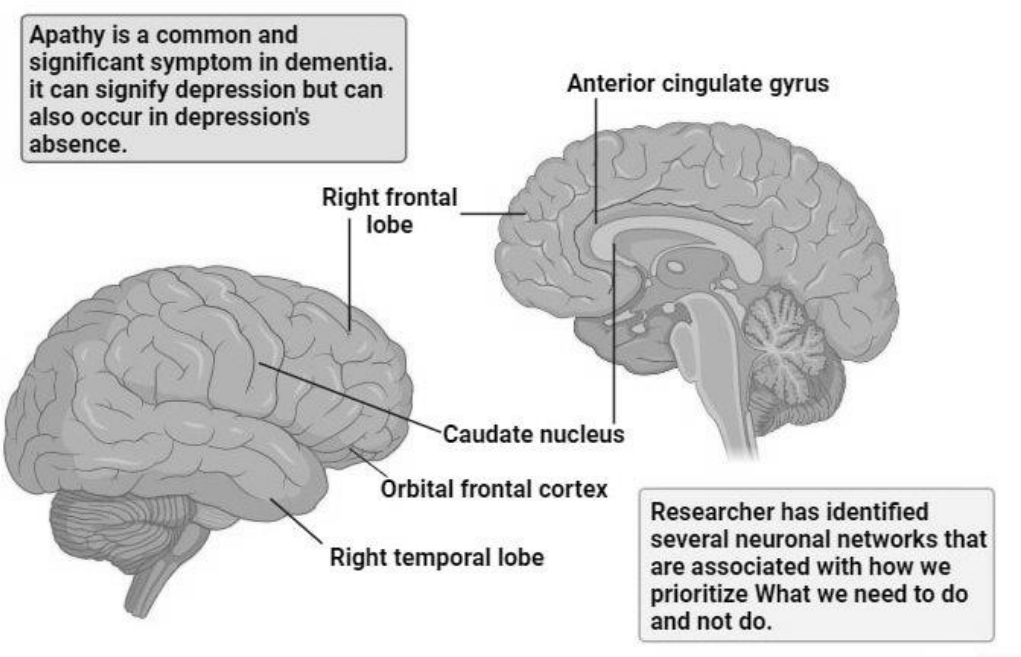

Fig 3: Apathy and its Localization in the Brain [59]

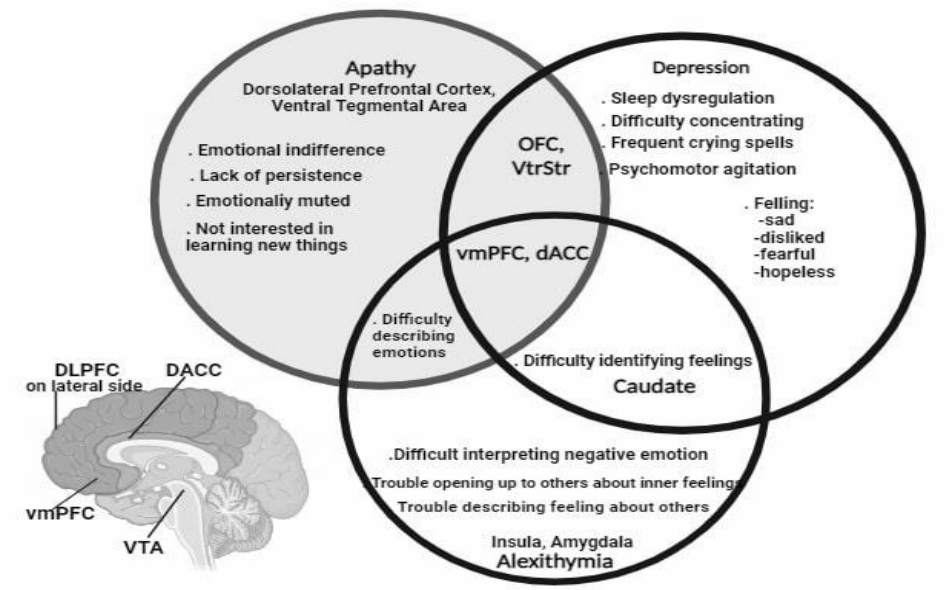

Fig 4: Symptom and neuroanatomical substrates of apathy, depression, and alexithymia

(VtrStr: Ventral striatum, vmPFC: ventromedial prefrontral, OFC: orbitofrontal cortex, dACC: dorsal anterior cingulated cortex, Cdt: caudate, DLPFC: Dorsolateral prefrontal cortex, VTA: ventral tegmental area) [60]

Assessment

The Scale for the Assessment of Negative Symptoms (SANS) [18] and the Positive and Negative Syndrome Scale (PANSS) [19] are two observer-rated first-generation scales that are most widely used in psychiatry to assess adverse or unpleasant symptoms. The scales do not assess emotions and thoughts; instead, they concentrate on observable behaviors. Furthermore, some of the items in their original negative symptoms subscales are now regarded as disorganized symptoms and cognitive symptoms [4]. However, factor assessments have found variables in both first-episode psychosis (FEP) and longer-term psychotic diseases that correlate to the experiencing and expressive domains [17,20], with little item variation across cultural boundaries [21]. One of the most accurate scales for use across disorders is the observer-rated apathy assessment measure or scale [22], which is a specific scale for apathy assessment. It is depicted in (Fig. 5). The Clinical Assessment Interview for Negative Symptoms [23] and the Brief Negative Symptom Scale [24], two observer-rated second-generation measures or scales, are in line with the existing domain and symptom framework and incorporate questions that assess apathy. Both scales evaluate visibly and blindly reported characteristics of apathy and other experience features or symptoms. The validity and reliability of apathy assessments based on self-reports is an area of concern. Later research has shown that there is no discernible difference between self- and observer assessments [26] despite prior studies arguing that they do [25] and instead of proposing that they do, tap on apathy's slightly different characteristics. The self-evaluation of adverse symptoms [27] evaluates motivation, whereas the pleasure and motivation scale-self-report [28] investigates the experiential area or domain. The self-evaluation of adverse symptoms [27] contains questions that assess apathy and have a five-factor structure that accords with the general definition of negative symptoms. In clinical practice, both are time-effective. In general, it is advised to assess apathy using second-generation negative or adverse symptom scales or particular measure tools [4]. Many of these scales could be used to evaluate apathy in conditions other than SSDs, like schizophrenia, bipolar illness, and depressive disorder [15]. In addition to information on evaluation or assessment, review articles by the European Psychiatric Association [4] and Lincoln et al [29] are other great resources of knowledge. Rarely are the secondary causes of apathy recognized. To reduce confounding in treatment trials, [4] it is essential to identify and assess potential secondary causes. For example, a decrease in depressive symptoms can be wrongly interpreted to have a therapeutic effect on primary apathy.

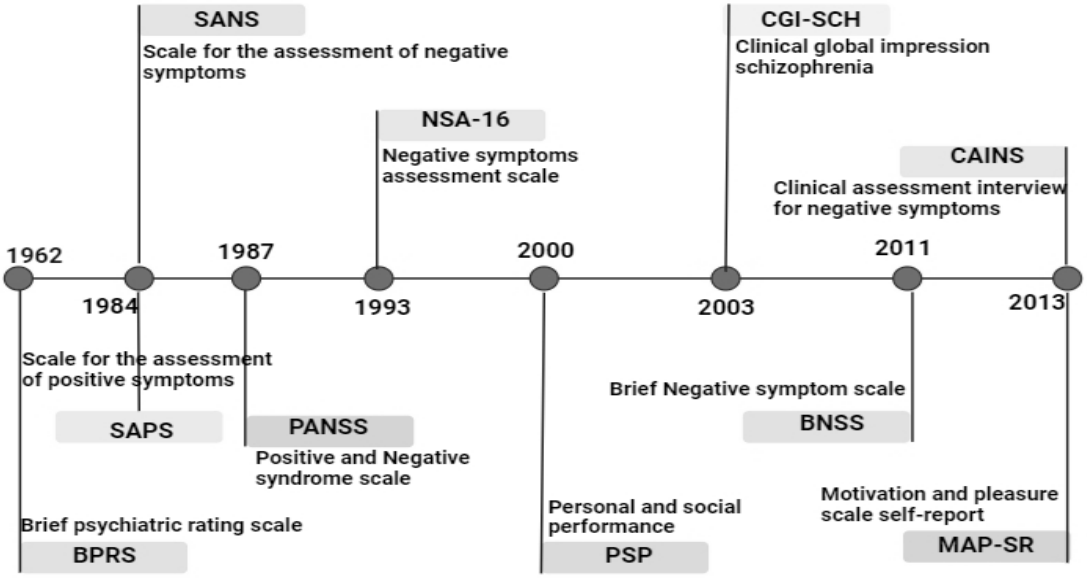

Fig 5: Schizophrenia Rating Scales or clinical rating scale for evaluating or assessing the symptoms of schizophrenia

Clinical rating scales are used to categorize the severity of the illness in schizophrenia and assess its symptoms. They can be considered as a means of quantifying clinical evaluation of the psychopathology that is present at the time and the evolution of symptoms through time. Scales are utilized in therapeutic settings as well, however, time restrictions associated with the delivery and the lack of qualified rater are limiting factors. The majority of the time, scales are used in clinical studies to judge how well schizophrenia treatments work. There is no agreement on which rating scale is the best, however, more recent scales have been devised to evaluate schizophrenia with an eye on ease in the clinical setting and a better assessment of negative symptoms [61].

Diagnostic criteria for apathy

Table 1: Criteria for diagnosing a neurological disease with apathy [62].

Diagnostic criteria for apathy in brain disorder
A reduction in goal-directed behavior or activity, thought, emotion, or social activity compared to the person's prior level of functioning.
Persisted for at least 4 weeks
Presence of at least two of the three dimensions: 1. Behavior and cognition 2. Emotion 3. Social interaction
Causes a significant impairment in one's personal, social, professional, or other key aspects of functioning
Not solely explained by or resulting from physical impairments, motor impairments, a decreased level of consciousness, the direct physiological effects of drugs, significant environmental changes, major changes in the person's environment , or other factors

TREATMENTS AND MANAGEMENT

Present Evidence

Since meta-analyses and systematic reviews frequently use RCTs to report negative or adverse symptoms as the global score of unifactorial negative symptoms measured with the PANSS or SANS, there isn't much evidence to support treating apathy in SSDs [30]. Adverse symptoms are also infrequently the major therapeutic goal. We will then give references to systematic reviews and randomized controlled trials that investigated the experiential domain of apathy therapy.

Psychosocial Treatments (Fig. 6)

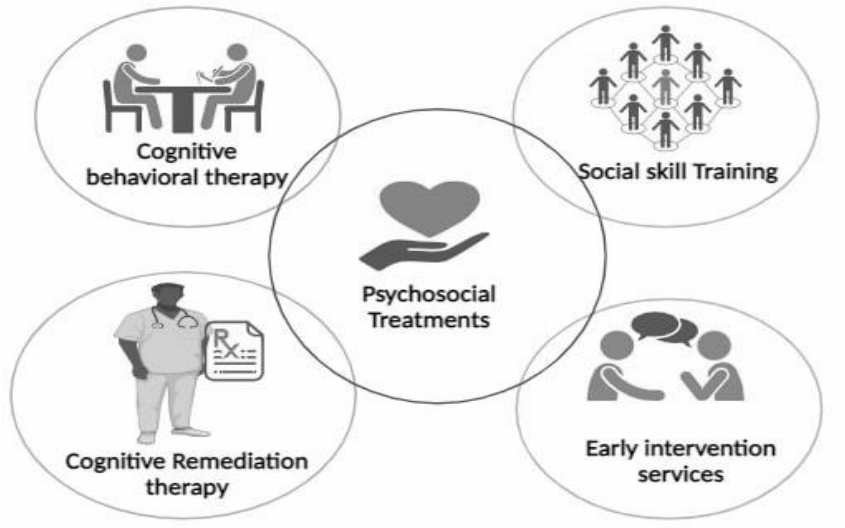

Fig 6: Psychosocial treatments for patients

Cognitive Behavioral Therapy (CBT)

Cognitive behavioral therapy for the effective treatment of negative symptoms (CBT) is an approach to improve burdensome or limiting thought and promote behavioral reinforcement. In an RCT (randomized controlled trials) examining the potency of CBTn for treating apathy in outpatients, it was discovered that standard treatment (ST) alone was ineffective compared to ST plus CBTn [31]. Six months after the end of the treatment, the effect remained [32]. The results may have been compromised by the CBT group's prolonged treatment period and lack of blinding of treatment allocation. Another Randomized controlled trial from the schizophrenia positive emotions program claims that participants who received the program (Cognitive Behavior Therapy) and standard care (TAU) saw a significant reduction in experiential domains at the end of the program and six months afterward, but only a decline in apathy. After participants whose treatment allocation was accidentally exposed were excluded, at six months, the therapies' impact on apathy was no longer significant or meaningful [33]. Cognitive behavioral therapy **(**CBT), but not cognitive remediation therapy (CRT), led to a minor improvement in experiential domain symptoms compared to conventional care, according to a limited but rigorous meta-analysis of RCTs that utilized a minimal threshold of adverse symptoms for study inclusion [34].

Social Skills Training

To reduce the danger of social rejection and social withdrawal, the primary objective of social skills training (SST) is to enhance interpersonal abilities, social interaction, and performance. Cognitive behavioral social skills training (CBT) was compared to an active control condition in one randomized controlled trial after nine months, the researchers from one RCT discovered that CBSST had a tepidly beneficial effect size improvement in the experiential domain [35]. Interpretation is limited by the lack of knowledge regarding the comparative effectiveness of the SST and CBT elements.

Cognitive Remediation Therapy

Cognitive remediation therapy (CRT) can address cognitive deficits that interfere with reward systems and motivation and reduce demoralizing thoughts. One randomized controlled trial showed a small but significant reduction in the experiential or practical domain when cognitive remediation therapy is paired with antipsychotic medication (AP), as contrasted to conventional therapy alone. Despite this, the authors viewed the results as preliminary because of the limited sample size [36]. Another RCT found that CRT plus AP significantly reduced apathy and the experiential domain when compared to constructive conduct training plus AP at 12 months post-treatment [37]. In a short pilot research trial, a novel social cognition remediation intervention (SoCIAL) was compared to a CRT that had previously been validated for functional and cognitive outcomes, and it was discovered that the SoCIAL intervention was the only one that led to improvements in the experiential domain [38]. It was shown in one study that when CRT was compared to a control condition, the experiential domain decreased, using individual data from four RCTs as the pooled data source. At the time of the follow-up, the effect, however, had disappeared [39].

Early Intervention Services

Early intervention services (EIS) offer specialized, low-barrier, minimally invasive, interdisciplinary services that combine pharmaceutical treatment with psychosocial therapies including cognitive behavioral therapy and family psychoeducation (Family psychosocial education therapy). Unifactorial unpleasant or negative symptoms are reduced early and persistently in intervention compared to control regions, according to studies that aim to reduce the time that people experience psychosis without receiving a diagnosis [40, 41]. In one randomized controlled trial (RCT), after two years of EIS, FEP participants were randomly assigned to undergo normal therapy or one additional year of EIS, and the effects of EIS on the experiential domain were examined. After treatment, the EIS group's experience domain score was significantly lower [42].

Biological Treatments

Antipsychotic Medication

Even though numerous metaanalyses indicated moderately positive results on unifactorial (single-factor) adverse outcomes for 2nd-generation antipsychotics yet not for 1st-generation antipsychotics when in contrast to placebo [43,44], no research has looked at apathy as an end measure. However, more recent medications, such as cariprazine, paliperidone, and pimavanserin, which are depicted in (Fig. 7 and Fig. 8) and don't directly influence receptors (dopamine) but have a preference for D3 receptors, might be significant [45]. Roluperidone, which predominantly targets 5HT2A and sigma2 receptors, was observed to considerably reduce experiential domain

symptoms in one phase 2b RCT compared to placebo [46], even though one another roluperidone RCT [47] showed a marginally significant reduction in the experiential domain.

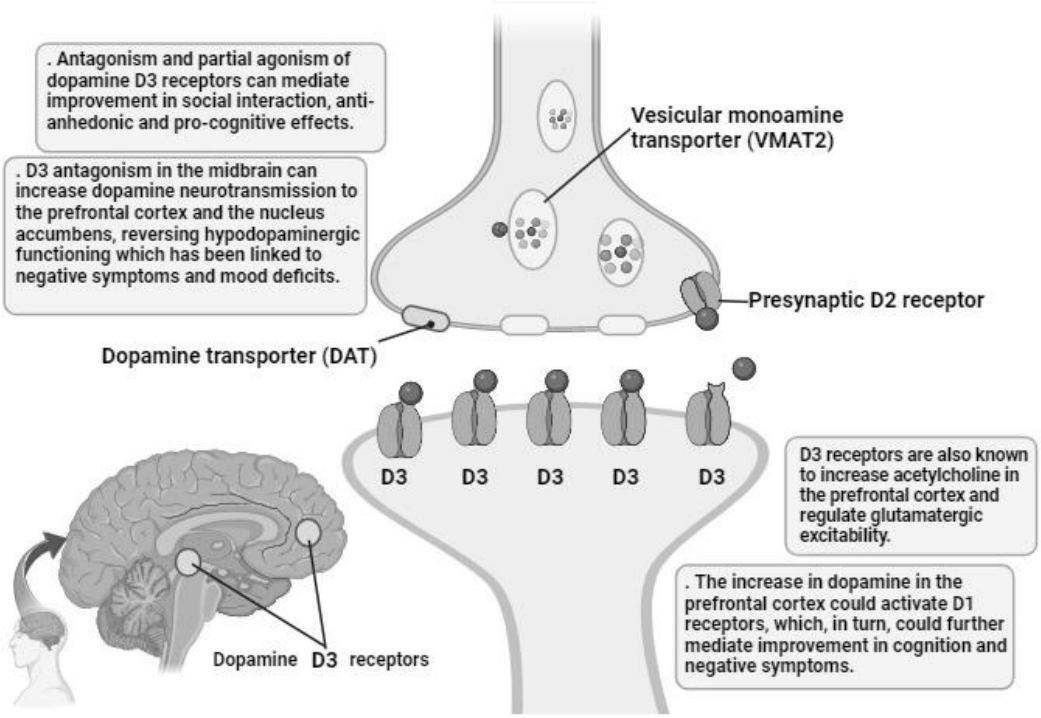

Fig 7: Dopamine (D3) Receptors' Function

D3 receptors are found in the mesolimbic area of the brain and regulate motivation, emotion, and reward. The control of unpleasant symptoms, mood, and cognition is thought to be aided by D3 receptors. [63]

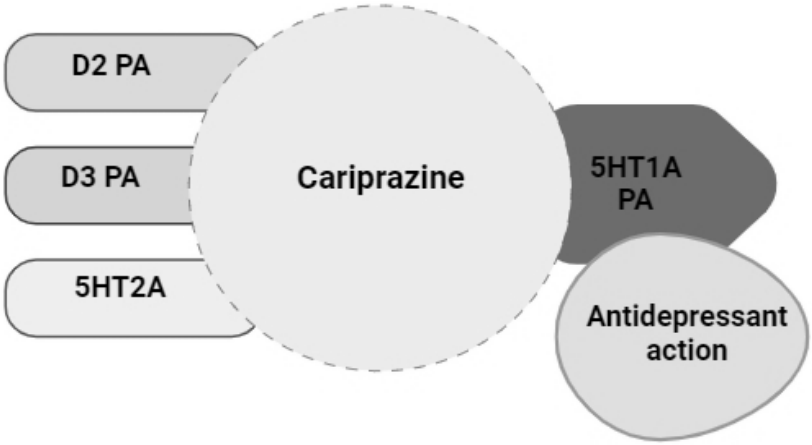

Fig 8: Cariprazine mode of action

The partial agonism of serotonin 5-HT1A receptors, antagonism of serotonin 5-HT2A receptors, and antagonism of dopamine D2/D3 receptors are thought to be the mechanisms through which cariprazine exerts its effects. Cariprazine has a high affinity for the D3 receptor, which is more potent than dopamine itself in terms of functional affinity. As of right now, cariprazine is the only antipsychotic that disables D3 receptors in the living brain where dopamine is present [64].

Adjunctive Medication

As adjunct therapy or adjunctive medication to antipsychotic pharmaceuticals (AP), several drugs have been evaluated [30]. Rasagiline [49], a monoamine oxidase B inhibitor, and citalopram [48], a selective serotonin reuptake inhibitor, were both compared to placebo in two RCTs, one of which was severely underpowered [48], and both showed a substantial decrease in the experiential domain and the apathy, respectively. The effects of anti-inflammatory, antibiotics medications, pro-dopaminergic, or pharmaceuticals altering oxytocin pathways or glutamate neurotransmission have not yet been investigated about apathy or the experiential domains.

Transcranial Stimulation

Repetitive transcranial magnetic stimulation (rTMS), which is illustrated in Fig. 9, is a technique for noninvasively stimulating or gently modulating particular prefrontal brain regions (brain cells) with brief magnetic pulses. In a well-powered, randomized, double-blind, sham-controlled randomized controlled trials with participants who primarily had unpleasant or negative symptoms, apathy was significantly reduced after rTMS compared to placebo [50], while no beneficial effects were observed on the experiential domain in another RCT [51]. A double-blind RCT showed that bilateral transcranial direct current stimulation significantly decreased the experience domain as compared to sham. However, no minimal threshold for the presence of negative symptoms was used, and secondary negative symptoms were not taken into account [52].

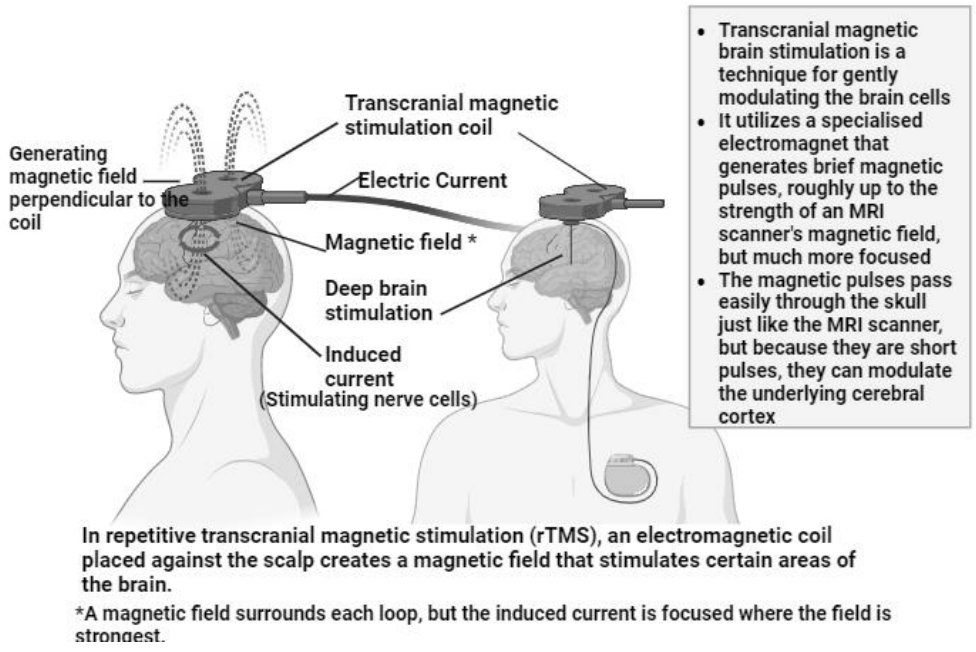

Fig 9: Repetitive Transcranial Magnetic Stimulation (rTMS) [65]

Future Directions

It makes sense to begin by undertaking therapy studies that focus on apathy with higher inclusion standards and improve the apathy evaluation for both primary and secondary levels. It might be beneficial to include a scale that measures both primary- and secondary indifference or apathy. The identification of unique treatment outcomes

may be made possible by reexamining the clinical data already collected using question formats that reflect the negative symptom domains [13]. Further research on the impacts of apathy is possible, although it is yet unclear how aerobic exercise, music therapy, mind-body therapies, and supplementary medication affect unifactorial unpleasant symptoms [30]. Actigraphy or smartphone registrations for ecological instantaneous evaluation may find fine-grained individual response profiles in addition to standard research methodologies [53]. Soon, transcranial cerebellar stimulation might be applied to medical treatment [54]. Additionally, ecological momentary treatments using a smartphone that aim to increase motivation and reward sensitivity [55] or simulations of real-world goal-directed activities in virtual reality [55] may potentially improve the effectiveness of treatment [56]. Future therapeutic and medical research must, without a doubt, concentrate on apathy and its harmful implications.

CONCLUSION

The specialized apathy evaluation instruments or 2nd-generation unpleasant or negative symptom scales, which are graded by clinicians, are currently the benchmark for assessing apathy in schizophrenia spectrum illnesses. These scales measure behavior, feelings, and thoughts, and therefore are more effective at recognizing symptoms that are related to actual experiences. Self-reports may provide more detail on subjective experience. Assessment scales cannot distinguish between primary and secondary causes of apathy, hence it is important to regularly evaluate potential secondary sources. Currently, apathy and the experience domain do not have a strong research basis for treatment. Cognitive behavioral therapy, Social skills training, and Cognitive remediation therapy, Repetitive Transcranial Magnetic Stimulation, paliperidone, and adjunctive medication are beneficial in preliminary studies. There are more hints that EIS improves successful outcomes.

Conflicts of interests

Proclaimed none (no conflicts of interest)

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Author's Contribution

G.S. designed the manuscript and developed the concept, S.P. and R.P did a critical revision of the article and R.R helped in drafting the article. Equal contributions have been made by each author.

Declarations

We affirm that each and every author of this scholarly endeavor made substantial contributions, and we have not excluded any authors who made significant contributions. We adhered diligently to the ethical norms set forth by our respective institution.

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References

1) Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. Lancet Psychiatry. 2018;5(8):664-77. doi: 10.1016/S2215-0366(18)30050-6, PMID 29602739.

2) Bègue I, Kaiser S, Kirschner M. Pathophysiology of negative symptom dimensions of schizophrenia–current developments and implications for treatment. Neurosci Biobehav Rev. 2020;116:74-88. doi: 10.1016/j.neubiorev.2020.06.004, PMID 32533996.

3) Kirschner M, Aleman A, Kaiser S. Secondary negative symptoms - a review of mechanisms, assessment and treatment. Schizophr Res. 2017;186:29-38. doi: 10.1016/j.schres.2016.05.003. PMID 27230288.

4) Galderisi S, Mucci A, Dollfus S, Nordentoft M, Falkai P, Kaiser S, et al. EPA guidance on assessment of negative symptoms in schizophrenia. Eur Psychiatry. 2021;64(1):e23. doi: 10.1192/j.eurpsy.2021.11, PMID 33597064.

5) Evensen J, Røssberg JI, Barder H, Haahr U, Hegelstad Wt, Joa I, et al. Apathy in first episode psychosis patients: a ten year longitudinal follow-up study. Schizophr Res. 2012;136(1-3):19-24. doi: 10.1016/j, PMID 22285655. schres.2011.12.019.

6) Fulford D, Piskulic D, Addington J, Kane JM, Schooler NR, Mueser KT. Prospective relationships between motivation and functioning in recovery after a first episode of schizophrenia. Schizophr Bull. 2018;44(2):369-77. doi: 10.1093/schbul/sbx096, PMID 28981811.

7) Faerden A, Friis S, Agartz I, Barrett EA, Nesvåg R, Finset A, et al. Apathy and functioning in first-episode psychosis. Psychiatr Serv. 2009;60(11):1495-503. doi: 10.1176/ps.2009.60.11.1495, PMID 19880468.

8) Strauss GP, Bartolomeo LA, Harvey PD. Avolition as the core negative symptom in schizophrenia: relevance to pharmacological treatment development. npj Schizophr. 2021;7(1):16. doi: 10.1038/s41537-021-00145-4, PMID 33637748.

9) Sauvé G, Brodeur MB, Shah JL, Lepage M. The prevalence of negative symptoms across the stages of the psychosis continuum. Harv Rev Psychiatry. 2019;27(1):15-32. doi: 10.1097/HRP.0000000000000184, PMID 30358662.

10) Lyngstad SH, Gardsjord ES, Engen MJ, Haatveit B, Ihler HM, Wedervang-Resell K, et al. Trajectory and early predictors of apathy development in first-episode psychosis and healthy controls: a 10-year follow-up study. Eur Arch Psychiatry Clin Neurosci. 2020;270(6):709-22. doi: 10.1007/s00406-020-01112-3, PMID 32130475.

11) Jabar LSA, Sørensen HJ, Nordentoft M, Hjorthøj C, Albert N. Associations between duration of untreated psychosis and domains of positive and negative symptoms persist after 10 years of follow-up: a secondary analysis from the OPUS trial. *Schizophr Res.* 2021;228:575–580. doi: 10.1016/j. schres.2020.11.027

12) Abram SV, Weittenhiller LP, Bertrand CE, *et al*. Psychological dimensions relevant to motivation and pleasure in schizophrenia. *Front Behav Neurosci.* 2022;16:827260–827260. doi: 10.3389/fnbeh.2022.827260

13) van der Meer L, Kaiser S, Castelein S. Negative symptoms in schizophrenia: reconsidering evidence and focus in clinical trials. *Br J Psychiatry.* 2021;219(1):359–360. doi: 10.1192/ bjp.2021.66

14) Zhao QF, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis. J Affect Disord. 2016;190:264-71. doi: 10.1016/j.jad.2015.09.069, PMID 26540080.

15) Strauss GP, Cohen AS. A transdiagnostic review of negative symptom phenomenology and etiology. Schizophr Bull. 2017;43(4):712-9. doi: 10.1093/schbul/sbx066, PMID 28969356.

16) Robert P, Lanctôt KL, Agüera-Ortiz L, Aalten P, Bremond F, Defrancesco M, et al. Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. Eur Psychiatry. 2018;54:71-6. doi: 10.1016/j.eurpsy.2018.07.008, PMID 30125783.

17) Messinger JW, Trémeau F, Antonius D, Mendelsohn E, Prudent V, Stanford AD, et al. Avolition and expressive deficits capture negative symptom phenomenology: implications for DSM-5 and schizophrenia research. Clin Psychol Rev. 2011;31(1):161-8. doi: 10.1016/j.cpr.2010.09.002. PMID 20889248.

18) Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. Br J Psychiatry Suppl. 1989;155(7):49-58. doi: 10.1192/S0007125000291496, PMID 2695141.

19) Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76. doi: 10.1093/schbul/13.2.261, PMID 3616518.

20) Stiekema AP, Liemburg EJ, van der Meer L, Castelein S, Stewart R, van Weeghel J, et al. Confirmatory factor analysis and differential relationships of the two subdomains of negative symptoms in chronically ill psychotic patients. PLOS ONE. 2016;11(2):e0149785. doi: 10.1371/journal.pone.0149785, PMID 26895203.

21) Khan A, Liharska L, Harvey PD, Atkins A, Ulshen D, Keefe RSE. Negative symptom dimensions of the positive and negative syndrome scale across geographical regions: implications for social, linguistic, and cultural consistency. Innov Clin Neurosci. 2017;14(11-12):30-40. PMID 29410935.

22) Clarke DE, Ko JY, Kuhl EA, van Reekum R, Salvador R, Marin RS. Are the available apathy measures reliable and valid? A review of the psychometric evidence. J Psychosom Res. 2011;70(1):73-97. doi: 10.1016/j, PMID 21193104. jpsychores.2010.01.012.

23) Kring AM, Gur RE, Blanchard JJ, Horan WP, Reise SP. The Clinical Assessment Interview for Negative Symptoms (CAINS): final development and validation. Am J Psychiatry. 2013;170(2):165-72. doi: 10.1176/appi.ajp.2012.12010109, PMID 23377637.

24) Kirkpatrick B, Strauss GP, Nguyen L, Fischer BA, Daniel DG, Cienfuegos A, et al. The Brief Negative Symptom Scale: psychometric properties. Schizophr Bull. 2011;37(2):300-5. doi: 10.1093/schbul/sbq059, PMID 20558531.

25) Selten JP, Wiersma D, van den Bosch RJ. Discrepancy between subjective and objective ratings for negative symptoms. J Psychiatr Res. 2000;34(1):11-3. doi: 10.1016/s0022-3956(99)00027-8, PMID 10696828.

26) Engel M, Lincoln TM. Concordance of self- and observerrated motivation and pleasure in patients with negative symptoms and healthy controls. Psychiatry Res. 2017;247:1-5. doi: 10.1016/j.psychres.2016.11.013, PMID 27863311.

27) Dollfus S, Mucci A, Giordano GM, Bitter I, Austin SF, Delouche C, et al. European validation of the self-evaluation of negative symptoms (SNS): a large multinational and multicenter study. Front Psychiatry. 2022;13:826465. doi: 10.3389/fpsyt.2022.826465, PMID 35173641.

28) Llerena K, Park SG, McCarthy JM, Couture SM, Bennett ME, Blanchard JJ. The Motivation and Pleasure Scale- Self-Report (MAP-SR): reliability and validity of a selfreport measure of negative symptoms. Compr Psychiatry. 2013;54(5):568-74. doi: 10.1016/j.comppsych.2012.12.001, PMID 23351831.

29) Lincoln TM, Dollfus S, Lyne J. Current developments and challenges in the assessment of negative symptoms. *Schizophr Res.* 2017;186:8–18. doi: 10.1016/j.schres.2016.02.035

30) Galderisi S, Kaiser S, Bitter I, *et al*. EPA guidance on treatment of negative symptoms in schizophrenia. *Eur Psychiatry.* 2021;64(1):e21. doi: 10.1192/j.eurpsy.2021.13

31) Grant PM, Huh GA, Perivoliotis D, Stolar NM, Beck AT. Randomized trial to evaluate the efficacy of cognitive therapy for low-functioning patients with schizophrenia. *Arch Gen Psychiatry.* 2012;69(2):121–127. doi: 10.1001/ archgenpsychiatry.2011.129

32) Grant PM, Bredemeier K, Beck AT. Six-month follow-up of recovery-oriented cognitive therapy for lowfunctioning individuals with schizophrenia. *Psychiatr Serv.* 2017;68(10):997–1002.

33) Favrod J, Nguyen A, Chaix J, Pellet J, Frobert L, Fankhauser C, et al. Improving pleasure and motivation in schizophrenia: a randomized controlled clinical trial. Psychother Psychosom. 2019;88(2):84-95. doi: 10.1159/000496479, PMID 30783071.

34) Riehle M, Böhl MC, Pillny M, Lincoln TM. Efficacy of psychological treatments for patients with schizophrenia and relevant negative symptoms: a meta-analysis. Clin Psychol Eur. 2020;2(3):e2899. doi: 10.32872/cpe.v2i3.2899, PMID 36398145.

35) Granholm E, Holden J, Link PC, McQuaid JR. Randomized clinical trial of cognitive behavioral social skills training for schizophrenia: improvement in functioning and experiential negative symptoms. J Consult Clin Psychol. 2014;82(6):1173-85. doi: 10.1037/a0037098, PMID 24911420.

36) Mahmood Z, Clark JMR, Twamley EW. Compensatory Cognitive Training for psychosis: effects on negative symptom subdomains. Schizophr Res. 2019;204:397-400. doi: 10.1016/j, PMID 30293693. schres.2018.09.024.

37) Ventura J, Subotnik KL, Gretchen-Doorly D, Casaus L, Boucher M, Medalia A, et al. Cognitive remediation can improve negative symptoms and social functioning in first-episode schizophrenia: a randomized controlled trial. Schizophr Res. 2019;203:24-31. doi: 10.1016/j.schres.2017.10.005. PMID 29128326.

38) Palumbo D, Mucci A, Piegari G, D'Alise V, Mazza A, Galderisi S et al.. SoCIAL – training cognition in schizophrenia: a pilot study. Neuropsychiatr Dis Treat. 2017;13:1947-56. doi: 10.2147/NDT.S136732, PMID 28790830.

39) Cella M, Stahl D, Morris S, Keefe RSE, Bell MD, Wykes T. Effects of cognitive remediation on negative symptoms dimensions: exploring the role of working memory. Psychol Med. 2017;47(15):2593-601. doi: 10.1017/S0033291717000757, PMID 28866985.

40) Melle I, Larsen TK, Haahr U, Friis S, Johannessen JO, Opjordsmoen S, et al. Reducing the duration of untreated first-episode psychosis: effects on clinical presentation. Arch Gen Psychiatry. 2004;61(2):143-50. doi: 10.1001/archpsyc.61.2.143, PMID 14757590.

41) Larsen TK, Melle I, Auestad B, Haahr U, Joa I, Johannessen JO, et al. Early detection of psychosis: positive effects on 5-year outcome. Psychol Med. 2011;41(7):1461-9. doi: 10.1017/S0033291710002023, PMID 20942996.

42) Chang WC, Kwong VW, Chan GH, Jim OT, Lau ES, Hui CL, et al. Prediction of motivational impairment: 12-month follow-up of the randomized-controlled trial on extended early intervention for first-episode psychosis. Eur Psychiatry. 2017;41:37-41. doi: 10.1016/j.eurpsy.2016.09.007, PMID 28049079.

43) Fusar-Poli P, Papanastasiou E, Stahl D, Rocchetti M, Carpenter W, Shergill S, et al. Treatments of negative symptoms in schizophrenia: meta-analysis of 168 randomized placebo-controlled trials. Schizophr Bull. 2015;41(4):892-9. doi: 10.1093/schbul/sbu170, PMID 25528757.

44) Osugo M, Whitehurst T, Shatalina E, Townsend L, O'Brien O, Mak TLA, et al. Dopamine partial agonists and prodopaminergic drugs for schizophrenia: systematic review and meta-analysis of randomized controlled trials. Neurosci Biobehav Rev. 2022;135:104568. doi: 10.1016/j.neubiorev.2022.104568, PMID 35131396.

45) Lobo MC, Whitehurst TS, Kaar SJ, Howes OD. New and emerging treatments for schizophrenia: a narrative review of their pharmacology, efficacy and side effect profile relative to established antipsychotics. Neurosci Biobehav Rev. 2022;132:324-61. doi: 10.1016/j.neubiorev.2021.11.032, PMID 34838528.

46) Harvey PD, Saoud JB, Luthringer R, Moroz S, Blazhevych Y, Stefanescu C, et al. Effects of Roluperidone (MIN-101) on two dimensions of the negative symptoms factor score: reduced emotional experience and reduced emotional expression. Schizophr Res. 2020;215:352-6. doi: 10.1016/j.schres.2019.08.029, PMID 31488314.

47) Davidson M, Saoud J, Staner C, Noel N, Werner S, Luthringer E, et al. Efficacy and safety of roluperidone for the treatment of negative symptoms of schizophrenia. Schizophr Bull. 2022;48(3):609-19. doi: 10.1093/schbul/sbac013, PMID 35211743.

48) Barnes TR, Leeson VC, Paton C, *et al*. Antidepressant Controlled Trial For Negative Symptoms In Schizophrenia (ACTIONS): a double-blind, placebo-controlled, randomised clinical trial. *Health Technol Assess.* 2016;20(29):1–46. doi: 10.3310/hta20290

49) Buchanan RW, Weiner E, Kelly DL, *et al*. Rasagiline in the treatment of the persistent negative symptoms of schizophrenia. *Schizophr Bull.* 2015;41(4):900–908. doi: 10.1093/ schbul/sbu151

50) Kumar N, Vishnubhatla S, Wadhawan AN, Minhas S, Gupta P. A randomized, double blind, sham-controlled trial of repetitive transcranial magnetic stimulation (rTMS) in the treatment of negative symptoms in schizophrenia. Brain Stimul. 2020;13(3):840-9. doi: 10.1016/j.brs.2020.02.016, PMID 32289715.

51) Bodén R, Bengtsson J, Thörnblom E, Struckmann W, Persson J. Dorsomedial prefrontal theta burst stimulation to treat anhedonia, avolition, and blunted affect in schizophrenia or depression - a randomized controlled trial. J Affect Disord. 2021;290:308-15. doi: 10.1016/j.jad.2021.04.053, PMID 34020205.

52) Lisoni J, Baldacci G, Nibbio G, Zucchetti A, Butti Lemmi Gigli E, Savorelli A, et al. Effects of bilateral, bipolar-nonbalanced, frontal transcranial Direct Current Stimulation (tDCS) on negative symptoms and neurocognition in a sample of patients living with schizophrenia: results of a randomized double-blind sham-controlled trial. J Psychiatr Res. 2022;155:430-42. doi: 10.1016/j.jpsychires.2022.09.011, PMID 36182772.

53) Kluge A, Kirschner M, Hager OM, Bischof M, Habermeyer B, Seifritz E, et al. Combining actigraphy, ecological momentary assessment and neuroimaging to study apathy in patients with schizophrenia. Schizophr Res. 2018;195:176-82. doi: 10.1016/j, PMID 29030262. schres.2017.09.034.

54) Hua JPY, Abram SV, Ford JM. Cerebellar stimulation in schizophrenia: a systematic review of the evidence and an overview of the methods. Front Psychiatry. 2022;13:1069488. doi: 10.3389/fpsyt.2022.1069488, PMID 36620688.

55) Novo A, Fonsêca J, Barroso B, *et al.* Virtual reality rehabilitation's impact on negative symptoms and psychosocial rehabilitation in schizophrenia spectrum disorder: a systematic review. *Healthcare (Basel)*. 2021;9(11). doi: 10.3390/healthcare9111429

56) Schlosser DA, Campellone TR, Truong B, *et al*. Efficacy of PRIME, a mobile App intervention designed to improve motivation in young people with schizophrenia. *Schizophr Bull.* 2018;44(5):1010–1020. doi: 10.1093/schbul/ sby078

57) Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. Schizophr Bull. 2006 Apr;32(2):214-9. doi: 10.1093/schbul/sbj053. Epub 2006 Feb 15. PMID: 16481659; PMCID: PMC2632223

58) Correll CU, Schooler NR. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. Neuropsychiatr Dis Treat. 2020 Feb 21;16:519-534. doi: 10.2147/NDT.S225643. PMID: 32110026; PMCID: PMC7041437
https://hdsa.org/wp-content/uploads/2015/02/Apathy-Talk.pdf

59) Fahed M, Steffens DC. Apathy: neurobiology, assessment and treatment. Clinical Psychopharmacology and Neuroscience. 2021 May 5;19(2):181. doi: 10.9758/cpn.2021.19.2.181
https://schizophrenialife.se/selection-of-schizophrenia-rating-scales/?

60) Ashcraft T, Breazeale L, Kahathuduwa C, Zhang B. Potential application of repetitive transcranial magnetic stimulation for apathy after traumatic brain injury: a narrative review. Brain Network and Modulation. 2022 Oct 1;1(4):148. DOI: 10.4103/2773-2398.365024

61) Correll CU, Schooler NR. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. Neuropsychiatr Dis Treat. 2020 Feb 21;16:519-534. doi: 10.2147/NDT.S225643. PMID: 32110026; PMCID: PMC7041437.

62) Stahl SM. Mechanism of action of cariprazine. CNS spectrums. 2016 Apr;21(2):123-7.
https://www.mayoclinic.org/tests-procedures/transcranial-magnetic-stimulation/about/pac-20384625