Anhedonia in Parkinson's Disease: An Overview

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This article presents an overview of anhedonia, the lowered ability to experience pleasure, in Parkinson's disease (PD). The definition, measurement, relationships with depression and apathy in PD, treatment, and hyperhedonia related to impulse-control disorder are presented and discussed. The authors present the value of a more circumscribed definition of anhedonia taking into account the distinction between anticipatory and consummatory anhedonia and propose various research approaches.

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Anhedonia is defined by a lowered ability to experience pleasure. It is recognized to be a core symptom of major depression, and approximately 30%–40% of subjects with Parkinson's disease (PD) have significant depression.[1] However, independently of the occurrence of depression in PD patients, anhedonia can be considered to be a specific mood disorder explained by dysfunction of the dopamine reward pathway secondary to the degenerative processes observed in PD, notably in the mesolimbic area.

Anhedonia, as well as other nonmotor symptoms of PD, is underrecognized and, consequently, undertreated. Moreover, nonmotor symptoms of PD lead to hospitalization and institutionalization.[2] However, and paradoxically, treatment of anhedonia in PD patients can be complicated by impulse-control disorders (ICD) such as excessive gambling or hypersexuality.

Surprisingly, although investigation of anhedonia in PD could have important clinical and therapeutic consequences, few studies on this subject have been published to-date.

The aim of this overview is to present and discuss the various studies investigating anhedonia in PD. Articles were initially retrieved from the personal database established by the first author, who has regularly published articles on anhedonia for several decades, and who regularly monitors the literature on this subject using, notably, the PubMed database with the keywords "anhedonia" or "anhedonia and Parkinson disease." This selection of literature has been found effective in

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psychiatric literature on anhedonia. However, the recent published review on anhedonia in PD,[3] which has used a wider PubMed search strategy, has found the same articles as the present overview. The following aspects will be discussed successively: definition and conceptual aspects of anhedonia in PD; assessment tools; clinical studies; and treatment, including its potential adverse effects and long-term evolution of PD. Finally, several recommendations for future research will be proposed.

DEFINITION AND CONCEPTUAL ASPECTS OF ANHEDONIA IN PD

Anhedonia is a neologism proposed by Théodule Ribot[4] in 1896 to define the lowered ability to experience pleasure, which is also called "hedonic deficit." This clinical characteristic has been notably described in depression, schizophrenia, and personalities prone to develop these two psychiatric disorders. In 1989, we proposed a distinction between anhedonia-state and anhedonia-trait.[5] Anhedonia-state refers to "anhedonia symptom" observed in various psychiatric disorders, with a similar course to that of the psychiatric disorder. Anhedonia-trait refers to a stable hedonic deficit found in psychiatric disorders before the onset of the disorder and that remains stable even if the psychiatric disorder recovers. Anhedonia-trait frequently characterizes subjects prone to develop schizophrenia or depression, and long-term prospective studies have shown that anhedonic non-psychotic subjects are prone to psychotic disorders.

Several anhedonias have been described, and authors classically distinguish sensorial or physical anhedonias from social or interpersonal anhedonias. This distinction appears to identify different patterns of behavior that have differential predictive validity in terms of individuals at risk for the later development of schizophrenia-spectrum disorders;[6] however, this distinction is not related to specific neurobiological pathways.

Several authors (see review by Gard et al.[7]) have recently proposed a more circumscribed definition of anhedonia, centered on the distinction between anticipatory and consummatory pleasures. Consummatory pleasure reflects the pleasure "in the moment," that is experienced while the subject is engaged in an enjoyable activity. Anticipatory pleasure is the pleasure that a subject experiences at the thought of a future event. Consummatory and anticipatory pleasures correspond respectively to the neuroscientists' concepts of liking and wanting in relation to reward. Moreover, several human studies have strongly suggested that dopamine could be involved in the anticipatory experience of pleasure, whereas other neurotransmitters (e.g., opioids) could be involved in the consummatory experience of pleasure.

Assessment Tools

Several rating scales have been proposed for evaluate anhedonia as well as apathy, and the Movement Disorder Society has commissioned a task-force to assess the psychometric properties of anhedonia and apathy scales in PD patients.[8] The task-force used a systematic literature search allowing structured assessment of the scales with regard to their descriptive properties, availability, content, use, acceptability, clinimetric properties, and overall impression in patients with and without PD.

Three anhedonia scales were identified for the review: the Snaith-Hamilton Pleasure Scale (SHAPS), and the revised Social (SAS) and Physical (PAS) Anhedonia Scales. The SHAPS[9] is a questionnaire that contains 14 statements with "Agree" or "Disagree" responses rated 0 or 1. The total score ranges from 0 to 14, where a high score indicates high anhedonia. Example of an item: "I would enjoy being with my family or close friends." The timeframe is the last few days.

The SAS[10] contains 40 items evaluating the social and interpersonal features of anhedonia with "Agree" or "Disagree" responses rated 0 or 1. The total score ranges from 0 to 40, where a high score indicates severe anhedonia. Example of an item: "I have often enjoyed long discussions with other people." The timeframe is not mentioned. The SAS and PAS evaluate a lifelong deficit of the hedonic capacity.

The PAS[10] contains 61 items evaluating the physical and sensorial features of anhedonia, with "Agree" or "Disagree" responses rated 0 or 1. The total score ranges from 0 to 61, where a high score indicates severe anhedonia. Example of an item: "The beauty of sunsets is greatly overrated." Taking into account the psychometric studies in non-PD and PD patients, the task-force only proposed use of the SHAPS scale and did not recommend the PAS and SAS, which lack face validity and are too long (61 and 40 items, respectively). In their review, the authors did not find any validation studies for the SHAPS in PD patients.

Since the review by Leentjens et al.,[8] two studies, one not cited by the authors,[11] and a more recent study,[12] examined the psychometric properties of the SHAPS in PD patients. In the study by Lemke et al.,[11] satisfactory

TABLE 1. Clinical Characteristics of Parkinson's Disease Patients in Anhedonia Studies

Authors	Pluck & Brown[22] 2002	Isella et al.[23] 2003	Lemke et al.[11] 2005	Santangelo et al.[12] 2009	Fujiwara et al.[24] 2011	Miura et al.[25] 2012
N	45	25	626	939	100	86
Controls	yes	yes	yes	yes	yes	no
Status	outpatients	?	both	both	outpatients	outpatients
% men	49	60	56	59	46	45
Age, years	66.4	67.4	67.7	67	69.3	72
Age at onset	?	?	?	?	?	64.9
Duration, years	10.3	4.9	?	6.8	6.7	7.2
Anhedonia, %	7	40[a]	45.7	?	10	16.3

Both: in- and outpatients; % anhedonia using Snaith-Hamilton Pleasure Scale cutoff score.
[a]anhedonia by the Physical anhedonia scale.

internal consistency and construct validity were found in 626 PD patients. In the study by Santangelo et al.,[12] high internal consistency, discriminant, and concurrent validities were reported in PD patients. Unfortunately, the test–retest reliability of the SHAPS has not been studied in PD patients.

However, a new anhedonia scale, the Temporal Experience of Pleasure Scale (TEPS[7]), including two subscales measuring anticipatory (TEPS-ANT) and consummatory (TEPS-CONS) pleasures, has been recently proposed and validated in various samples of normal or psychiatric subjects.[13] To our knowledge, the TEPS has not been studied in PD patients. Several studies have examined the correlations between the TEPS and the PAS, SAS, or SHAPS in nonclinical or clinical samples.[7,14,15] Significant correlations were found, in various nonclinical or clinical samples, between the PAS and the TEPS-ANT or TEPS-CONS, although the SAS was significantly correlated with only the TEPS-ANT. For the SHAPS, only one study reported a significant correlation with the TEPS-CONS in a nonclinical sample, but significant correlations with the TEPS-CONS or TEPS-ANT in psychiatric subjects.[15] The PAS and SHAPS can therefore measure both consummatory and anticipatory anhedonias, although the SAS can only measure anticipatory anhedonia.

CLINICAL STUDIES

To our knowledge, only six studies have investigated anhedonia in PD patients by use of anhedonia scales (Table 1). Before these six studies, six papers that did not use anhedonia scales suggested that anhedonia could characterize depressed or nondepressed PD patients.

Fibiger[16] has suggested that the high incidence of depression in PD patients, characterized by anhedonia as a cardinal feature, could be explained by damage to the reward-related systems. This damage was explained by degeneration of the mesolimbic and mesocortical dopamine projections found in PD.

Cantello et al., in 1989,[17] studied the euphoric response to intravenous methylphenidate (MP) in four groups of PD patients (PD patients with major depression, PD patients without major depression, non-PD patients with major depression, and control subjects without central nervous system or psychiatric disease). PD patients with major depression showed a significant lack of sensitivity to the euphoriant effects of MP, in comparison with the other three groups. This result was interpreted as a consequence of dysfunction of the reward-related dopamine systems in PD patients with major depression, characterized by anhedonia as the main symptom.

Wolfe et al.[18] showed that patients with PD, Alzheimer's disease, or major depression have a distinct pattern of neuropsychological deficits associated with low homovanillic acid (HVA) in the cerebrospinal fluid (CSF). Compared with subjects with high CSF HVA, subjects with low CSF HVA presented a particular neuropsychological profile linked to low dopamine and characterized by extrapyramidal motor signs, bradyphrenia in neuropsychological tests, and depression.

Taking into account that the right cerebral hemisphere is more involved with the experiences of emotion, Fleminger[19] reported that PD patients with markedly asymmetrical symptoms, more severe on the left side of the body (LHF), have greater anxiety and depression than PD patients with markedly asymmetrical symptoms, more severe on the right side of the body (RHF).

The authors concluded that the results support the notion that alterations in the neurochemical balance of the brain (more marked depletion of dopamine in the right striatum) contribute to the pathogenesis of depression and anxiety in PD patients.

Bermanzohn and Siris[20] have suggested that akinesia (characterized by slowed motor activity), anhedonia with depressed mood, and reduced affective range and cognitive impairment could be common to parkinsonism, retarded depression, and negative symptoms of schizophrenia.

Recently, Winograd-Gurvich et al.[21] reviewed the current literature on negative symptoms in schizophrenia, melancholic depression, and PD. Negative symptoms refer to reduction in normal functioning and encompass apathy, anhedonia, flat affect, avolition, social withdrawal, and psychomotor retardation. In schizophrenia, melancholic depression, or PD, negative symptoms were characterized by motor impairment (akinesia), cognitive impairment, and apathy. Neuropathological and biochemical findings have been found to be similar in the three disorders, suggesting comparable impairment in the functioning of frontostriatal-limbic circuits.

The six previous papers that did not use anhedonia scales therefore strongly suggested the following conclusions: 1) anhedonia could be one of the main characteristics of PD, with or without associated major depression; 2) anhedonia could be explained by the high incidence of depression in PD; 3) anhedonia in PD could be induced by the reduction of central dopaminergic activity, notably in the regions that mediate the reward response; 4) anhedonia is associated with akinesia, apathy, and cognitive impairment in PD; 5) anhedonia could be more severe in left-sided PD.

Several studies have explored the role of anhedonia in PD using anhedonia scales notably testing the validity of the previous five conclusions.

Pluck and Brown[22] studied the levels of apathy in 45 PD outpatients (49% men, mean age: 66.4 years; mean duration of PD: 10.3 years) and 17 similarly disabled patients with osteoarthritis. Apathy and anhedonia were rated with the Apathy Evaluation Scale (AES) and the SHAPS, respectively. Using the cut-off of 3, three PD patients (7%) and no osteoarthritis patients were anhedonic. Using the cut-off of 38 on the AES to divide PD patients into a High Apathy group (N=17) and a Low Apathy group (N=28), the High Apathy group was more severely anhedonic (12%) than the Low Apathy group (4%).

Isella et al.[23] compared the PAS in 25 consecutive PD patients (60% men; mean age: 67.4 years; mean disease duration: 4.9 years) and 25 healthy subjects. The authors used the Italian version of the PAS, which is inversely scored, with higher scores indicating less severe anhedonia. PD patients had lower scores on the PAS than controls; 40% of PD patients were anhedonic versus 0% of controls. No significant correlations were reported between the PAS and depression or apathy rated by the Brink Geriatric Depression and Marin Apathy Scales, respectively. In this study, the scoring of the PAS has been reversed. It would be preferable to keep the original scoring to avoid confusion. In psychiatric literature, the PAS is one of the most used anhedonia scales, and the authors did not change the scale coding to allow study comparisons and metaanalyses.

Lemke et al.[11] studied the psychometric properties of the German version of the SHAPS in 626 PD inpatients or outpatients (56% men; mean age: 67.7 years). Using the Depression subscale of the Short Parkinson's Evaluation Scale (SPES), this population comprised 138 depressed PD patients and 488 nondepressed PD patients, with 286 (45.7%) anhedonic (SHAPS >3) patients and 340 (54.3%) non-anhedonic (SHAPS <3) patients. Anhedonic PD patients had more severe motor and nonmotor symptoms as rated by the SPES subscales than non-anhedonic PD patients. The SHAPS score was not significantly different between healthy subjects and nondepressed PD patients, but depressed PD patients had significantly higher SHAPS scores than nondepressed PD patients: 79.7% of depressed PD patients (N=110) and 36.1% (N=176) of nondepressed PD patients were anhedonic. SHAPS scores were significantly correlated with the SPES total score and the subscales of the SPES rating motor functioning, psychopathology, depression, and activities of daily living. No significant correlations with SHAPS scores were observed when partial correlations were calculated, using either the SEPS Depression or SPES Motor Functioning subscales.

After the addition of pramipexole and at the end of a 9-week maintenance period (T_2), PD patients were re-evaluated. At T_2, the prevalence of anhedonia was 25.5% (45.7% of at T_1) and 45.3% (74.3% of T_1) for all PD patients and depressed PD patients, respectively. Moreover, the percentage of nondepressed PD patients markedly increased between the two evaluations.

Santangelo et al.[12] studied the Italian version of the SHAPS in 150 consecutive PD patients (42.7% men) with

major depression (N=74) according to DSM-IV criteria or without depression (N=76) and in healthy subjects (N=74). Depressed PD patients had significantly higher scores on the SHAPS than healthy subjects and nondepressed PD subjects. Nondepressed PD patients also had significantly higher scores on the SHAPS than healthy subjects. In a large sample of PD patients (N=939; 59% men; mean age: 67 years; mean disease duration: 6.8 years), the authors reported significant correlations between the SHAPS and rating scales evaluating frontal functions, mental state, and depression.

Fujiwara et al., in 2011,[24] examined 100 consecutive PD outpatients (46% men; mean age: 69.3 years; mean disease duration: 6.74 years) at follow-up visits during regular treatment with anti-Parkinson drugs and 111 age-matched controls. The subjects filled out the Japanese version of the SHAPS and the Self-Rating Questionnaire of Depression (SRQ-D); 10% of PD patients and 2.7% of controls were considered to be anhedonic (SHAPS $\geq$3). Anhedonic PD patients had significantly higher scores on the SRQ-D than nonanhedonic PD patients. Depressed PD patients (N=46) also had significantly higher scores on the SHAPS than nondepressed PD patients (N=54). However, the authors compared the frequency of anhedonia between groups treated with each anti-Parkinson drug and groups without each drug. A significant difference was observed only for pramipexole. Among the 100 PD patients, 25 received pramipexole, and 75 did not receive this drug. The frequency of anhedonia was 0% and 13% among subjects treated and not treated with pramipexole, respectively.

The last study, Miura et al., in 2012,[25] used the Japanese version of the SHAPS in 86 consecutive outpatients (45% men; mean age: 72.01 years; mean duration of illness: 7.2 years) with a clinical diagnosis of PD. There was no control group. The Hoehn and Yahr scale rated disease severity; 16.3% of the subjects had scores $\geq$3 on the SHAPS. There were no relationships between the SHAPS scores and age, age at onset, duration of illness, gender, disease severity, and treatment (L-dopa, entacapone). PD patients receiving pramipexole had lower SHAPS scores than patients who did not receive this treatment. Multiple-regression analysis exploring the predictors of SHAPS scores showed that pramipexole was a significant negative influencing factor on the SHAPS score (reducing anhedonia) and that both disease severity and entacapone were positive influencing factors (increasing anhedonia).

The six previous studies that used anhedonia scales in PD patients therefore have led to the following conclusions:

1. The frequency of anhedonia ranged from 7% to 45.7%. One explanation for the different prevalences could be related to the transcultural validity of the SHAPS. All authors used the same cut-off score as that determined for the original version,[9] although different foreign-language versions of the scale were used. It is important for foreign-language versions of the scale to calculate the corresponding cut-off scores, rather than using the cut-off score calculated in the English version of the SHAPS. Another possible explanation could be the mean age or proportion of inpatients, which could explain high levels of anhedonia. These explanations cannot be confirmed, as the mean age of the PD patients in the six samples was not different (e.g., 69.3 years in the Fujiwara et al. sample;[24] 67.7 in the Lemke et al. sample[11]), and the various samples included outpatients. The prevalence of anhedonia in PD patients was also independent of the rate of depression. In the study by Lemke et al.,[11] the prevalence of anhedonia and depression were 45.7% and 22%, respectively, whereas in the study by Fujiwara et al.,[24] the prevalence of anhedonia and depression were 10% and 46%, respectively.
2. All studies that used the SHAPS showed a strong association between anhedonia and depression in PD, but no concordance concerning the level of anhedonia in nondepressed PD patients was observed between the various studies.
3. Anhedonia and apathy are closely related.
4. Pramipexole, a dopamine agonist active on D_2, D_3, and D_4 receptors, has a high affinity for D_3 receptors and could be a strong anti-anhedonic agent, but it is not clear that this effect can be distinguished from the antidepressant action of this medication.[26,27]

THERAPEUTICS

Witt et al., in 2006,[28] investigated the differential effects of L-dopa and subthalamic stimulation on depressive symptoms and anhedonia in PD patients. Fifteen PD patients were examined before and 3 months after bilateral electrode implantation in the subthalamic nucleus for deep brain stimulation. Patients received an average L-dopa equivalent daily dosage of 915 mg before surgery

TABLE 2. Treatment of Anhedonia, as Rated by the Snaith-Hamilton Pleasure Scale (SHAPS), in Parkinson's Disease

	Lemke et al.[11]	Witt et al.[28]	Fujiwara et al.[24]	Miura et al.[25]
L-dopa		+		
Pramipexole	+		+	+
Entacapone				—
Subthalamic stimulation		0		

+: decreased anhedonia; −: increased anhedonia; 0: no effect.

and 409 mg 3 months after surgery. The Beck Depression Inventory (BDI) and the SHAPS were used to evaluate depression and anhedonia, respectively. A significant effect of medication and stimulation was observed on the total score of the BDI. A significant effect of medication was observed on the score of the SHAPS, but no significant effect was observed for stimulation.

Several animal experiments have suggested that dopamine agonists, notably agonists with an affinity for D_3 receptors, could have antidepressant and anti-anhedonic effects. Clinical studies (e.g., Lemke et al.[11]) using the SHAPS studies in PD patients have suggested that pramipexole could have anti-anhedonic effects. Consequently, as SHAPS is correlated with TEPS-ANT or TEPS-CONS in psychiatric subjects, we can hypothesize that medication has an effect on anticipatory and consummatory forms of anhedonia in PD patients (see Table 2).

On the other hand, ICD, notably characterized by hyperhedonia, has been described in PD patients receiving dopamine-replacement therapy, mainly dopamine agonists, particularly those with a preferential affinity for D_3 receptors.[29] ICD is frequently characterized by hypersexuality, pathological gambling, and shopping, and can be associated with punding and dopamine-dysregulation syndrome. Punding is a compulsion to perform repetitive mechanical tasks, such as sorting, collecting, or assembling and disassembling common items. ICD can be treated by reduction of dopaminergic treatment, but a recent case report suggests that suicide could be a complication after withdrawal of the D_3 receptor-agonist that had induced hypersexuality.[30]

Anhedonia and Long-Term Evolution of PD

There is a considerable debate concerning the relationship between dementia and Lewy bodies (DLB), the second most common form of dementia after Alzheimer's disease (AD), and dementia occurring as a late manifestation of PD. Clinical criteria for DLB have focused on psychotic symptoms, but one study (Rockwell et al.[31]) compared 26 autopsy-confirmed cases of DLB with 26 autopsy-confirmed cases of "pure" AD. The DLB cases were matched individually with AD cases for gender, ethnicity, and Mini-Mental State Exam score at baseline evaluation. Using retrospective psychiatric interview, the authors reported five psychiatric symptoms (hallucinations, delusions, anxiety, anhedonia, and loss of energy) that were significantly more common in DLB patients than in AD patients. The prevalence of anhedonia was 76% and 37% in DLB and AD patients, respectively, and this difference was not attributed to any known risk factors, as the two groups were not significantly different in terms of age at onset of dementia, level of education, personal history of major neuropsychiatric disorder, or intake of psychotropic medications. Unfortunately, in this study, the distinction between consummatory and anticipatory anhedonias was not taken into account, although high levels of anticipatory anhedonia could characterize PD patients at risk for developing DLB.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Anhedonia is one of the most frequent psychiatric symptoms in PD and cannot be totally explained by depression. Anhedonia and apathy are associated, and anhedonia can be decreased, particularly by treatment with D_3 agonists. Hyperhedonia is a characteristic of impulse-control disorder (ICD).

Several questions remain unresolved and could be addressed by using a better definition of anhedonia that distinguishes consummatory and anticipatory anhedonia. Anticipatory anhedonia could be a specific hedonic deficit characterizing depressed or nondepressed PD patients. Consummatory anhedonia could be a hedonic deficit characterizing only endogenomorphic depressed PD patients. The relationship between apathy and anhedonia could be explained only by the anticipatory component of anhedonia. Anticipatory anhedonia could

be treated by dopamine therapy, and anticipatory hyperhedonia could characterize ICD.

In view of the strong relationship between anticipatory anhedonia and dopamine deficit, anticipatory anhedonia may characterize non-PD subjects prone to develop this condition. Prospective studies on subjects at high risk for PD could test this hypothesis. One hypothesis could be that subjects with essential tremor and anhedonia, notably, anticipatory anhedonia, have a higher risk of developing PD than subjects with essential tremor without anhedonia. Moreover, this risk would be higher in subjects with atypical essential tremor with predominantly left-sided tremor. The exploration of hedonic deficits in PD has a strong heuristic value, allowing, notably, the definition of a more restricted form of the disease, the prevention of severe side effects of treatment by L-dopa or a dopamine agonist, and the identification of vulnerability factors to PD or DLB.

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