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Serotoninergic brain dysfunction in neuroendocrine tumor patients: A scoping review

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ABSTRACT

Introduction: Neuroendocrine tumors (NETs) are rare and malignant neoplasms characterized by their potential to produce metabolically active substances with the capacity to bring about clinical syndromes. The clinical expression of serotonin-producing NETs is known as carcinoid syndrome (CS). The synthesis of serotonin in the brain is dependent on tryptophan availability. At the central level, serotonin is indispensable for mood, anxiety, and sleep regulation. In CS patients, around 60% of all tryptophan is reported to be consumed by tumor cells for the peripheral synthesis of serotonin, increasing the risk of a central deficiency and thus psychiatric disorders.
Materials and methods: This manuscript reviews the existing literature about psychiatric disorders associated with NETs and addresses the safety of psychiatric drugs in these patients. A systematic search of the biomedical literature was performed using the following databases: PubMed, Embase, CINAHL (EBSCO), PsycInfo (OVID), and Cochrane CENTRAL (Wiley). The database search included articles published between January 1965 and February 2021. Relevant information were charted using a calibrated charting-form.
Results: Twenty-two articles were included in the present review. The overall population size of the studies came to 3319 patients. All patients presented a confirmed diagnosis of NET. The information about the presence of CS was confirmed in 351 cases. The psychiatric symptoms reported included mood disturbances (including, depression and anxiety), psychoses, impulse control disorders and sleeping alterations. We also evaluated the presence of cognitive impairments in NET patients. Finally, we summarize the available data regarding the safety of psychiatric drugs in this setting.
Conclusions: Psychiatric disorders among NET patients are poorly recognized, and therefore have received very little research attention. As a result, no standardized algorithm is presently available. Our findings support detailed psychiatric evaluation in NET patients, especially in those presenting CS and symptoms suggestive of psychiatric involvement. Not only do cognitive impairment and psychiatry symptoms negatively impact health-related quality of life in cancer patients, they can also reduce survival rates.

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1. Introduction

1.1. Neuroendocrine tumors and carcinoid syndrome

Neuroendocrine tumors (NETs) constitute a relatively rare form of neoplastic disease. They most commonly arise in hormone secreting tissue of the gastrointestinal tract and in the lungs, where they form solid malignant tumors [1]. The incidence and prevalence of NETs is increasing, partly due to earlier detection and improved therapy, which prolong survival times. Between 1973 and 2012, a 6.4-fold age-adjusted increase in their incidence was observed (6.98 per 100,000 patients) [1].

NETs are typically associated with a well-differentiated morphology, a low proliferation index, and an indolent behaviour. A peculiar characteristic of NETs is their potential to synthesize and secrete a wide range of metabolically active substances into the systemic circulation (e.g. hormones and amines, such as bradykinins, tachykinins, prostaglandins, and histamine) of which serotonin is the most prominent [2]. NETs may involve more than 15 different neuroendocrine cell types, each secreting a different hormone, thereby leading to a wide spectrum of clinical syndromes [3]. The diagnosis of these syndromes is established when a specific combination of signs and symptoms matches the clinical presentation of a patient and confirmed once corresponding elevated hormone levels are established [4]. Thus, according to the international guidelines, NET can be classified as functioning or non-functioning [5]. The slow development of NETs usually means that survival is not limited by tumor burden, but instead by the complications elicited by the high levels of specific hormones secreted.

Carcinoid syndrome (CS) is the clinical expression of serotonin-producing NETs – the most common NET-associated ectopic hormonal syndrome. In these patients, mostly serotonin, but also histamine and the kinin peptides, enter the systemic circulation without being first subjected to hepatic metabolism, thus determining the clinical manifestations. In fact, the primary tumors leading to CS comprise those not draining into the portal system and those involving hepatic metastasis, thereby able to bypass hepatic metabolism. A highly sensitive and specific (both exceeding 90%) test for CS involves a urine examination for 5-hydroxyindoleacetic acid (5-HIAA) – the primary end-product of serotonin metabolism [6].

Approximately 30% of NET patients (mainly those with their primary origin in the small intestine, but also with pancreatic or bronchial NET) present CS. The excessive production of serotonin by tumor cells in these patients leads to a wide range of manifestations that may include: secretory diarrhea (in about 70% of patients), flushing (in 90% of cases), venous telangiectasia (in 25% of cases), abdominal pain, pellagra (in 5%), bronchospasm (in about 15%), carcinoid crisis, and neuropsychological symptoms [6]. Fibrosis is also considered a characteristic trait of CS: chronic exposure to high levels of blood serotonin could also induce fibrogenic responses in distant or local organs, potentially resulting in mesenteric fibrosis and carcinoid heart disease (CHD) [7,8].

The pathogenesis of CS has received much research attention over the last few decades, and several important improvements have been achieved regarding its management [9], chiefly through the implementation of multidisciplinary tumor board evaluations.

Long- acting somatostatin analogues (SSAs) inhibit serotonin secretion and are the mainstay medical treatment for controlling symptomatic CS [10]. The high efficacy of SSA treatment has been corroborated by several studies [11–14]. For instance, in the observational SymNET study, 76% of NET-CS patients receiving a six-month treatment with lanreotide reported being “completely” or “rather” satisfied regarding the control of diarrhea, and 73% reported being “completely” or “rather” satisfied with the control of flushing following treatment with lanreotide for more than three months [15]. Despite the initial effectiveness of SSAs as a treatment for CS, symptoms are frequently reported to reoccur over the course of the disease [16].

The recent approval of telostristat (Xermelo®) by the US Food and Drug Administration (FDA) and the European Commission and its introduction into clinical practice has represented a significant advancement in this setting. In fact, two phase III randomized clinical trials have shown telotristat ethyl, a novel inhibitor of tryptophan hydroxylase – the rate-limiting enzyme in serotonin biosynthesis – to be well tolerated and highly effective in patients with refractory CS. The first study, the TELESTAR trial, regarded CS patients for whom SSA therapy was ineffective (defined as having ≥4 BMs per day while receiving SSAs). It found telotristat ethyl treatment to cause a significant decrease in both u5-HIAA levels and the frequency of bowel movements (BM) [17]. Similarly, TELECAST (an international, multicenter, randomized, double-blind, placebo-controlled phase III, trial) assessed the safety and efficacy of telotristat ethyl in patients with symptomatic CS who either had <4 BMs/day with concomitant SSA therapy or were not receiving concomitant SSA therapy [18]. The key finding of this study was the demonstration of a significant decreasing in u5-HIAA from baseline in patients treated with telotristat ethyl, compared to placebo.

Furthermore, peptide radioreceptor therapy (PRRT), implemented using radio-labeled somatostatin analogues, has showed encouraging results, both in controlling tumor growth and in keeping hormonal syndromes under control [19,20].

Other medical approaches have been employed, such as liver-directed therapies (radioembolization, chemoembolization/embolization) [21–24], surgical debulking, and radiofrequency ablation [25], providing some level of relief for the patients. Unfortunately, data coming from randomized clinical trials are not available for these therapeutic approaches.

Finally, in relation to life expectancy, thanks to hormonal secretion controlling treatments, patients with well differentiated NET and CS can now expect to live for several years with a median overall survival time for all patients of 9.3 years (112 months), but their life could be undermined by recurrent acute and chronic CS complications, thus

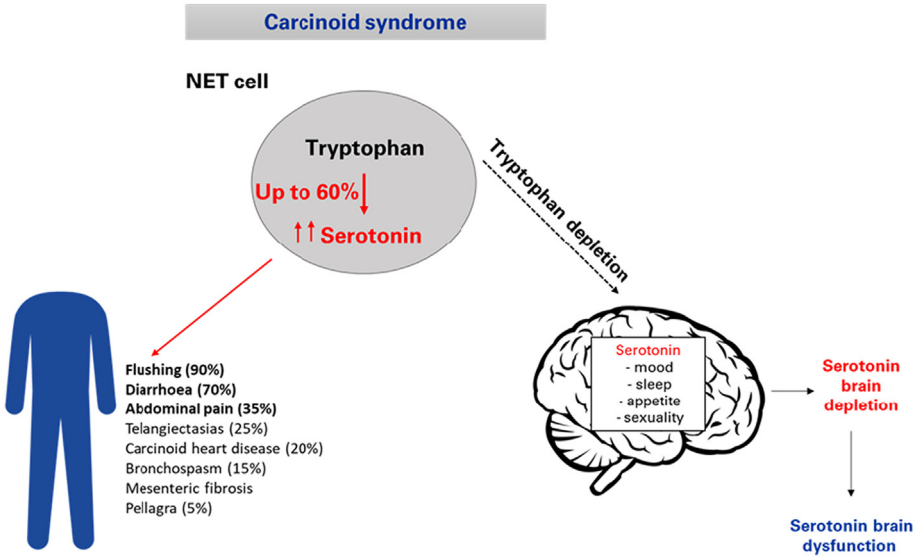

Fig. 1. Pathophysiology of serotoninergic brain depletion in carcinoid syndrome patients.
Carcinoid syndrome (CS) is the most frequent ectopic hormonal syndromes in serotonin-producing NETs. CS include a wide range of manifestations, as well as fibrotic complications. Brain serotonin synthesis depends on availability of its precursor, the essential amino acid tryptophan, which in CS patients is consumed up to 60% for serotonin synthesis by tumor cells. As a consequence, a serotoninergic brain depletion with an increased risk for developing a broad spectrum of psychiatric disorders should be carefully considered in NET patients with CS.

with the potential to severely impact patients' quality of life (QOL) and overall survival rate [26].

1.2. Pathophysiology of serotoninergic brain depletion in NET patients with carcinoid syndrome

Serotonin, or 5-hydroxytryptamine (5-HT), a monoamine, is the key neurotransmitter involved in several physiological functions. In the central nervous system (CNS), it is synthesized in the serotoninergic neurons of the raphe nuclei of the brainstem; in the peripheral nervous system (PNS), on the other hand, where it primarily affects the digestive tract, it is synthesized by specialized enteroendocrine cells in the gastrointestinal tract called enterochromaffin cells. In the CNS, serotonin plays an essential role in the regulation of mood, sexual desire and activity, anxiety, sleep, appetite, and body temperature.

Under physiological conditions, peripheral serotonin is unable to cross the blood-brain barrier, thus cerebral serotonin synthesis depends on the bioavailability of the essential amino acid tryptophan – its dietary precursor [27]. The unbound portion of circulating tryptophan can access the CNS and be converted into serotonin by means of enzymatic hydroxylation and decarboxylation [28]. In patients with NET and CS, the body's metabolism of tryptophan is altered, with approx. 60% of all dietary tryptophan being consumed by the tumor cells for serotonin synthesis [29]. Hence, when CS escapes diagnosis and is left untreated, patients may suffer from a range of adverse events caused by tryptophan deficiencies, such as the development of pellagra, also triggered by niacin (vitamin B3) deficiency, characterized by rough scaly skin, angular stomatitis, and glossitis [30]. At the CNS level, the peripheral consumption of tryptophan could bring about its depletion in the brain, resulting in a serotonergic deficit (Fig. 1) with an increased risk for developing a broad spectrum of psychiatric problems, from mood disorders (above all, depression and anxiety) to psychotic, eating or sexual disorders [31,32]. Moreover, brain serotonin depletion might underlie the plethora of cognitive impairments encountered in NET patients with CS [33,34].

Serotonergic antidepressants, including selective serotonin reuptake inhibitors (SSRIs), are the mainstay of depression treatment in cancer patients. SSRIs inhibit the reuptake of serotonin by the presynaptic terminal; the prolonged presence of serotonin in the synaptic cleft results in increased postsynaptic receptor activation, and therefore in altered postsynaptic neurotransmission. However, other side-effects of CS result from enhanced serotonergic activity at the level of the GI tract, which bring about increased GI motility [35]. The potential overlap between SSRIs adverse effects and CS symptoms (above all diarrhea) has led to the suggestion that serotonergic antidepressants could exacerbate CS and should be carefully administered in patients with NETs [36]. Unfortunately, data concerning the indications and the safety of SSRIs in NET patients are very limited.

1.2.1. The aims of this scoping review

The purpose of our exploratory project was to conduct a scoping review to systematically map the available data on psychiatric symptoms and disorders in NET patients with CS, with the aim of providing evidence-based practical guidance on diagnosis and management of this challenging disease.

Three areas of clinical utility were examined:

(i) Characteristics of psychiatric disturbances in NET disease: the epidemiological and clinical features, and prognostic implications.
(ii) Diagnostics: instruments and psychiatric tools.
(iii) Therapeutics: safety and efficacy of psychiatric agents (i.e. serotoninergic antidepressants) in this population.

2. Materials and methods

All published data concerning diagnosis, surveillance, management, and follow-up care of psychiatric symptoms and disorders in NET patients were retrieved by a systematic search of the biomedical literature conducted using the following databases: PubMed, Embase, CINAHL (EBSCO), PsycInfo (OVID), and Cochrane CENTRAL (Wiley). The database search included articles published between January 1965 and February 2021. Relevant journals, references in key articles, and other appropriate documents and expert reports were also hand-searched to supplement the electronic searches.

The overall search strategy consisted of three parts that were then combined with Boolean operators. The first two parts were intended to identify all citations regarding pharmacological anti-depressive

agents, using first broader and then narrow subject headings and keyword terms describing this class of drugs. In part two, we searched for subject headings and keywords describing "mood disorders", "anxiety", "depression", "mania", "impulse control disorders", "psychosis", "cognitive impairment" combined with the Boolean operator AND to concepts describing drug therapy in general. These two first search sets were then combined as synonymous concepts for antidepressants using the Boolean operator OR.

For the third part of the search strategy, subject headings and keyword terms describing carcinoid tumors/syndrome were combined as synonyms using the Boolean operator OR. In PubMed, CINAHL, and Cochrane CENTRAL, the "carcinoid" concept search term string was expanded to also include broader NET terms (i.e. "neuroendocrine tumors" "neuroendocrine neoplasms", "neuroendocrine tumors", "neuroendocrine carcinomas" and "carcinoid"). This third part of the search strategy was then combined to the former two, using the Boolean operator AND, in order to obtain a final set of citations that mentioned both the carcinoid and the anti-depressive agent concepts.

In all databases, controlled vocabulary was used whenever available, with the exception of Cochrane CENTRAL, where only keywords were used. We searched for articles in all available languages and with no date or publication type restrictions. However, we selected only articles in English. The PubMed and Embase search results were limited to "Human" with the intent of excluding pre-clinical studies.

Two authors (APP and ALS) independently reviewed titles and abstracts, excluding irrelevant articles and duplicates. Then they retrieved the full texts for all remaining articles. Disagreements were resolved by the two authors in an iterative process.

According to the scoping review design, a calibrated charting-form was developed to collect all key information relevant to the review questions. Two reviewers (APP and ALS) independently charted data for each study and continuously update the data-charting form in an iterative process.

3. Results

A total of 4236 studies identified from the literature review and the undertaken pooled data analysis were screened; 101 were assessed for eligibility on the basis of title and among them 54 were declined after analysing the abstract. Of selected the 47 full-texts, 22 articles were included (the details pertaining to the eligible studies are reported in Table 1 and in Fig. 2). Among these 22 studies, 9 (40.9%) were prospective studies, 4 retrospective studies (18.1%) and 9 (40.9%) were case reports (the different types of studies and the neuropsychological symptoms are depicted in Fig. 3). The overall population size of the studies came to 3319 patients. All patients presented a confirmed diagnosis of NET. The information about the presence of CS was confirmed in 351 cases.

The psychiatric symptoms reported included mood disturbances (e.g. depression and anxiety), psychoses, impulse control disorders, and sleeping alterations. We also focused on the presence of cognitive impairments. Finally, we collected the available data about the safety of psychiatric drugs in this setting.

3.1. Mood and anxiety disorders

An outdated study reported a higher rate of depression in NET patients compared with a population of patients with different forms of cancer (50% vs 15–20%) [37]. Higher levels of anxiety and depression were detected in patients with gastrointestinal (GI) NETs with CS than in those that did not involve serotonin-secreting tumors.

A recent retrospective, population-based, observational cohort study, including 2721 NET patients, demonstrated moderate-to-severe scores for anxiety (30%–40%). The proportion of moderate-to-severe anxiety decreased by 10% within 6 months of diagnosis and then remained stable over time [38].

A prospective, observational study, evaluated health-related quality of life (HRQoL) and mood of 120 NET patients with CS. HRQoL, as measured by the PROMIS-29 questionnaire, found that patients had worse scores if compared with the general population across all measured domains. In fact, PROMIS questions revealed that depression anxiety and insomnia were present in a significant percentage of the included patients (17.7%, 24.2% and 34.9%, respectively) [39].

Another prospective analysis of 111 NET patients was aimed to investigate anxiety and depression (HADS) prevalence in this population. Overall, 30% of participants had anxiety and 20% had depression and they had significantly lower physical and emotional well-being compared to the general population [40].

A prospective study included 44 pancreatic NET patients and 46 age-matched controls. Four questionnaires were administered to the

Table 1
Studies on psychiatric symptoms in NETs.

Reference	Study design	N of patients	Carcinoid syndrome	Neuropsychological domain
Hanna SM, 1965 [48]	Case report	1	N = 1 (100%)	Psychosis
Major LF, 1973 [37]	Retrospective	22	NA	Depression
Trivedi S, 1984 [49]	Case report	1	NA	Psychosis
Aoki A, 1997 [53]	Case report	1	N = 0 (0%)	Bipolar disorder
Larrsson G, 2001 [46]	Prospective	24	N = 20 (83%)	Anxiety, depression
Russo S, 2004 [47]	Prospective	20	N = 20 (100%)	Impulse control disorder, Depression
Kito S, 2005 [51]	Case report	1	N = 0 (0%)	Psychosis
Simbera Z, 2005 [44]	Case report	1	N = 0 (0%)	Anxiety, depression
Furse RM, 2008 [36]	Case report	1	N = 1 (100%)	Depression
Kohen I, 2008 [50]	Case report	1	N = 1 (100%)	Psychosis
Pezzilli R, 2009 [41]	Prospective	44	N = 0 (0%)	Depression
Chambers AJ, 2010 [33]	Prospective	21	N = 21 (100%)	Cognitive functions impairment
Pasieka JL, 2014 [34]	Prospective	36	N = 36 (100%)	Cognitive functions
Nobels A, 2016 [45]	Case report	1	N = 1 (100%)	Anxiety, depression
Fröjd C, 2017 [42]	Prospective, comparative	36	NA	HRQoL, psychosocial functions
Goswami S, 2017 [43]	Prospective, comparative	111	NA	Anxiety, depression
Shi DD, 2017 [54]	Retrospective	52	N = 52 (100%)	Depression
Isenberg-Grzeda, 2018 [55]	Retrospective	92	N = 16 (17%)	Depression
Adams J, 2018 [39]	Prospective	120	N = 120 (100%)	Anxiety, depression and insomnia
Beesley VL, 2018 [40]	Prospective	111	N = 62 (56%)	Anxiety, depression
Hallet J, 2019 [38]	Retrospective, observational cohort study	2721	NA	Anxiety
Boujan N, 2020 [52]	Case report	1	N = 0 (0%)	Psychosis, bipolar disorder

Abbreviations: HRQoL:health-related quality of life, NA: not available.

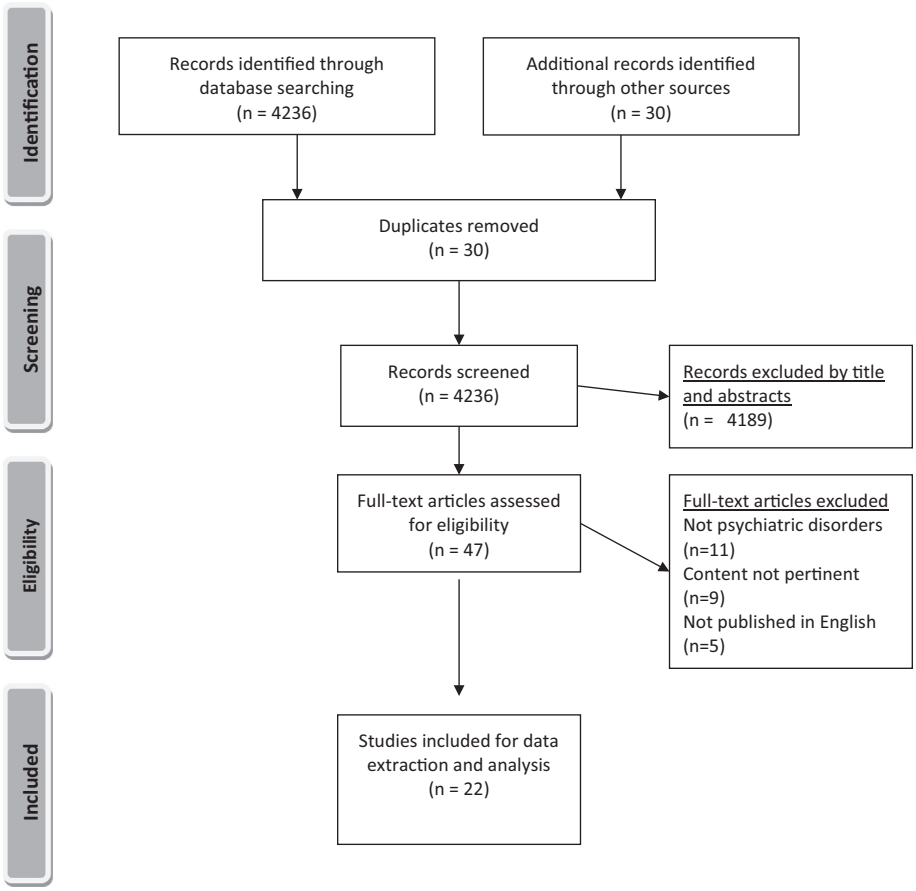

Fig. 2. Literature search workflow.

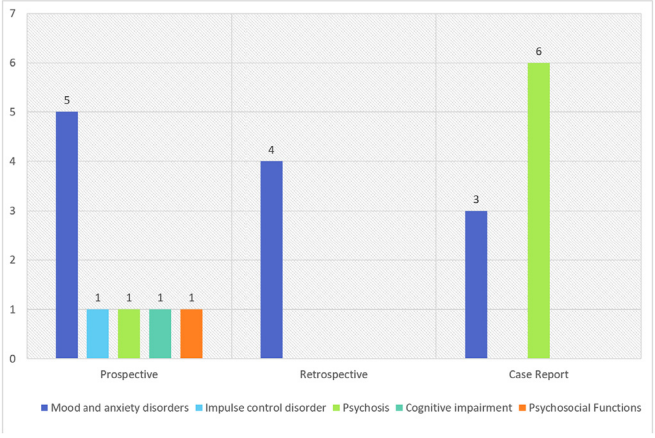

Fig. 3. Type of study and Neuropsychological domain.

patients: 12 items General Health Questionnaire (GHQ-12) for nonpsychotic psychiatric disorders, State Trait Anxiety Inventory (STAI) Y-1 and Y-2 for anxiety and BDI-II for depressive symptoms to explore the psychological aspects of the disease. Notably, this study detected eight patients (18.2%) with moderate depression and 9 (20.5%) with mild depression [41].

A prospective, case-control study including 36 NET patients showed worse scores for depression (according to the HADS scale), anxiety, and sleep quality than matched controls. In this study, 32 patients (89%) presented depressive symptoms, which constituted the most prevalent symptom of emotional distress [42].

Furthermore, a prospective analysis of 207 patients diagnosed with the inherited Multiple endocrine type 1 (MEN-1) syndrome has been carried out. MEN1-specific questionnaire and the PROMIS-29 were utilized in this study, showing that Individuals with MEN-1 reported statistically significant worse anxiety and depression, than general population ($p < 0.001$) [43].

Some case reports described severe depression and anxiety onset in patients with NET [36,44,45]. 2 of the three cases resulted associated with CS. In one case full recovery of the depressive episode was achieved under treatment with daily escitalopram 5 mg without any increase in diarrhea, nausea or flushing (which are the clinical manifestations of CS) [45].

Conversely, the results of another study failed to confirm higher rates of psychiatric symptoms in NET patients, reporting relatively low levels of depression (according to the HADS scale) [46]. Similarly, a depressive symptomatology that consisted of only mild dysthymia was reported in only 5 out of the 20 patients enrolled (15%) in another study [47].

3.2. Impulse control disorders

A prospective study, which enrolled 20 patients with NET and CS, demonstrated a high rate of decreased impulse control. Augmented aggressive impulses causing disturbed social functioning due to verbal aggression in social or job-related situations was reported in 75% of patients ($n = 15$; 8 males and 7 females), which strongly differentiated them from the control group. This symptomatology reached Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria, and the

patients were diagnosed as having a personality change due to a medical disorder [47].

3.3. Psychoses

Psychotic symptoms were described in three case reports of patients with CS. Two of the three cases considered were admitted because of psychiatric symptoms in the absence of a known psychiatric history [48–50]. Additionally, one case describes a MEN-1 patient, presenting with psychotic episode, characterized by auditory and visual hallucinations, delusions, and catatonia [51].

Two case reports of pancreatic NET patients with functioning tumor with a hormonal syndrome different from CS (glucagonoma and insulinoma, respectively) were reported to be associated to bipolar disorder. The first case presented delusions of grandeur and persecution, in the context of bipolar affective disorder diagnosis [52]. The second case presented agitation, stereotyped movements, and incoherent and uncooperative behaviour. Notably, the treatment of the primary tumor did not alleviate his psychiatric symptoms of manic-depressive disorder [53].

3.4. Cognitive impairment

Besides the aforementioned studies on psychopathology presentations in patients with NETs, others have attempted to evaluate the association between CS and cognitive impairment. A sample of 21 patients with proven CS was evaluated by analysing the results of the Multiple Ability Self-Report Questionnaire (MASQ) and other cognitive tests, and revealed the delayed recall of verbal memory and visual perceptual impairment, whereas the immediate recall of verbal memory, visual memory, language, and executive function all fell within physiological ranges [33].

In a cross-sectional study involving 36 patients with CS, and 20 age/sex/educational-matched healthy volunteers with non-neuroendocrine cancer as controls. Greater cognitive dysfunction was reported in the CS patients in relation to all cognitive domains: initiation, processing speed, visual memory, cognitive efficiency, and delayed verbal recall compared with controls. Marginally slower mental flexibility was observed compared with the control cancer group [34]. In particular, patients with CS demonstrated lower capacities in initiation, processing speed, visual memory, cognitive efficiency, and delayed verbal recall compared with healthy volunteers. That said, patients with non-NET cancer were also affected by cognitive dysfunctions compared with the healthy population; CS patients performed significantly worse in tests of delayed recall ($P = 0.03$), and were slightly slower in tests of mental flexibility tests ($P = 0.097$) compared with patients with non-NET cancer. Hence, the study showed that CS patients are characterized by cognitive impairments that are distinct to those suffered by non-NET cancer patients and the population at large.

3.5. Biomarkers

Only in one study was a correlation between CS markers and psychiatric disorders reported. Russo and colleagues detected a negative correlation between plasma tryptophan levels in CS patients and tumor endocrine activity evaluated as 5-HIAA excretion in a 24 h time window. This result supports the notion that carcinoid tumors reduce plasma tryptophan levels. The study did not find plasma tryptophan levels to correlate with disturbances in impulse control. They suggested that the lack of any correlation may be due to physiological fluctuations in plasma tryptophan [47].

In another study, patients' scores for depression at 12 months correlated with plasma concentrations of chromogranin A ($p < 0.05$) [46].

3.6. Safety of psychiatric treatments

Two retrospective studies have summarized the use of serotonergic antidepressants in NET patients [54,55]. In these reports, these therapies appear safe in almost all NET patients irrespective of the presence CS. However, the number of patients with adverse effects was so low that a thorough appraisal of any potential demographic or clinical predictors was not possible.

The first included 52 NET patients, all with CS, treated at Dana-Farber/Brigham and Women's Cancer Center receiving serotonergic antidepressant therapy between 2003 and 2016 following CS diagnosis. In the majority of the patients of this study, serotonergic therapies were ascertained to be safe for the treatment of depressive and anxiety symptoms. Less than 10% of patients reported a mild exacerbation of certain symptoms (flushing, diarrhea, and bloating) following therapy commencement [54].

The second study included 92 well-differentiated NET patients prescribed antidepressants from January 2008 through to April 2015. Only 16 of the study patients presented carcinoid syndrome (17%). The median time that those with CS received the therapy was 11.6 months (total range: 0–121 months) ($n = 16$) vs 14.3 months (total range: 0–172) for those without CS ($n = 76$). The therapy was ceased in 31 cases (33.7%), however, the reason was unspecified in most cases ($n = 18$; 58%). None of the patients developed carcinoid syndrome while undertaking antidepressant therapy. No patients developed carcinoid crisis [55].

4. Discussion

In daily clinical practice, the neuropsychiatric alterations commonly observed in NET patients, which include a wide variety of symptoms, from slight irritability to anxiety, depression, psychosis and sleep disorders, can lead to social dysfunctioning [42,56–59]. The hypothesis that CS patients suffer serotonergic brain dysfunction due to the peripheral over-consumption of the essential amino acid tryptophan is widely supported. However, to date, only few prospective studies have investigated the epidemiological and clinical features of the psychiatric symptoms and disorders presented by NET patients with CS, and retrospective data are highly inconsistent.

The present review provides the most complete and detailed overview of the current state of knowledge on serotonergic brain dysfunction that afflicts a minority of NETs patients. The 22 studies analysed provide an overall sample size of 3319 patients, all with a confirmed diagnosis of NET. The diagnosis of CS was confirmed in 351 cases, representing only 10.5% of all the included patients. However, 351 cases of CS and psychiatric symptoms represents a relatively large number of cases considering the rarity of NETs and that CS accounts only for a part of NET patients. Notably, the majority of the studies included in our analysis had a prospective or retrospective design (59%).

Considering the main findings provided by the literature discussed herein, more research attention needs to be devoted to the psychiatric symptoms and psychological distresses of patients diagnosed with NET, especially if accompanied by CS. Overall, the rate of neuropsychiatric symptoms in patients with NET is significantly higher than in control groups [37,43,47,60]. Indeed, in NET patients, the effects of circulating serotonin secreted by NET cells combines synergistically with the excessive allostatic load caused by the malignancy itself. In addition to the classic physical symptoms of CS, psychiatric symptoms should be taken into account, especially those related to adjustment disorder, such as anxiety, depression, and sleep disruption. An increased appreciation of the potential psychiatric symptoms of CS would render the oncologist more aware of the importance of referring the patient to the psychiatrist for in-depth assessment and diagnostic processing, and aid the identification of the most appropriate, patient-tailored therapeutic approach. For instance, to evaluate anxiety and depression symptoms in cancer patients, the psychiatrist should favour the use one of the

scales indicated by *liaison* psychiatry, such as the Hospital Anxiety and Depression Scale (HADS) [61], over other available assessment tools. This scale is already widely used in oncology and is particularly suitable for use in patients with physical comorbidities [62–65]. This scale could also be used by the specialist to follow the patient's clinical progress over time. Initiating a dialogue between the specialists involved is a priority for a more comprehensive and careful multidisciplinary approach to neuroendocrine pathology, also bearing in mind drug interactions and the management of side effects. Finally, an important finding is that the most common antidepressant drugs appear to be safe and free of any significant adverse outcomes in this particular clinical population, as reported by a recent systematic review focused on psychiatric therapy in NET patients [66].

However, an important limitation is also related to the high heterogeneity of the included studies (in terms of type of study, analysed population and measures used in the reported studies). Furthermore, another limit of our review was the exclusion of non-English articles.

5. Conclusions

Currently, the recognition and the management of psychiatric symptoms in NET patients involves processes that are still being developed. The epidemiology, the pathogenesis, and the clinical presentation of serotoninergic brain dysfunction due to serotonin-secreting tumors are still not well characterized, reflecting the lack of supporting literature. The safety and efficacy of serotoninergic antidepressants seem to be acceptable, but further studies are required to investigate the predictive value of socio-demographic, clinical and pharmacological variables for possible side-effects. Moreover, the possibility remains that patients with anxiety, depression, and sleep disorders due to CS might benefit from other psychiatric drugs (e.g. atypical antipsychotics), even if their efficacy and safety have not yet been fully assessed, other than in individual case studies. Subsequently, psychiatric disorders among NET patients remains a poorly recognized and scarcely studied topic; indeed, a standardized algorithm has yet to be put forward. According to our main findings, an accurate psychiatric and cognitive evaluation should be encouraged in NET patients, especially in those with CS, since both cognitive impairment and psychiatry symptoms can significantly influence health-related quality of life. Therefore, this key aspect should be better evaluated in further studies to understand how the diagnosis, treatment, and follow-up of this population of patients could be improved.

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Author contributions

All authors contributed to the development of the publication and maintained control over the final content. The authors did not receive professional help with the preparation of the manuscript.

CRediT authorship contribution statement

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Declaration of Competing Interest

ALS, APP, IP, ET, EP, NC, MPB, RLP, FO have no conflicts of interest to declare.

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