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Pineal Gland Abnormalities and the Relationship of Melatonin to the Development and Symptom Severity of Schizophrenia: An Integrative Review of the Literature

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PINEAL GLAND ABNORMALITIES AND THE RELATIONSHIP OF MELATONIN TO THE DEVELOPMENT AND SYMPTOM SEVERITY OF SCHIZOPHRENIA: AN INTEGRATIVE REVIEW OF THE LITERATURE

By

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Abstract

The purpose of this thesis is to critique the literature focusing on the role of pineal gland volume and function and the development of schizophrenia by asking the question, "What is the relationship between pineal gland physiologic function and development and symptom severity of schizophrenia? It is crucial that health care providers continue advocate for better understanding of schizophrenia in order to develop a more appropriate treatment and relive the suffering of those with schizophrenia. A review of published literature focusing on the pineal glands association with schizophrenia was performed using several databases including: ScienceDirect, PubMED, Google Scholar, Cumulated Index to Nursing and Allied Health Literature (CINAHL), and Elton B. Stephens Co. (EBESCO). Key search terms included: Pineal gland, melatonin and schizophrenia, pineal gland and schizophrenia, sleep and schizophrenia, melatonin and treatment for schizophrenia, alternative treatments for schizophrenia, and pineal volume and schizophrenia. Based on current researching findings, it is my prediction that the chief consensus among the literature will be that physiologic abnormalities often coincided with schizophrenia, but do not indicate the severity of the disease or seem to have a strong correlation to the cause of the disease. It is also my prediction that alternative therapies will be beneficial in reducing symptoms severity, and adverse effects cause by psychiatric medications.

Dedication

Dedicated to individuals afflicted with schizophrenia.

Acknowledgements

I am especially grateful for opportunity to produce and publish a body of work so close to my heart. There have been many wonderful individuals who have supported and guided me during the writing of this literature review. First, I would like to thank my Thesis Chair, Dr. Angeline Bushy, for her continued patience and guidance during this arduous task. Her kindness and understanding for all of life's road bumps was not insignificant to my completion of this thesis. To Dr. Leslee D'Amato-Kubiet, my committee member, thank you for your support and assistance in pushing me to produce my best work. I would also like to extend my gratitude to my close friend, primary editor, and cheerleader: Cassandra Hanlon. Without her this thesis would have never come to fruition.

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Introduction

Diagnosed commonly in late adolescence or early adulthood, schizophrenia affects around one percent of the population worldwide. By this estimate, schizophrenia and schizophrenia related disorders affect an estimated 3 million people in the United States (Videbeck, 2019). Rather than a singular disease, schizophrenia is considered as a syndrome or disease process with variability in symptoms, presentations, and severity. Symptoms of schizophrenia are classified into two general categories: positive or negative. In either category, symptoms can impose life changing challenges, making it difficult for the individual to have a fully functioning lifestyle. Fortunately, pharmacology interventions and community-based care have made it possible for many individuals with schizophrenia to successfully integrate and lead healthy lives. Still, the exact pathophysiology for the disease is unknown.

A recent theory describes irregularities in the pineal gland as a potential contributing factor for this disorder. The pineal gland, sometimes called the “third eye” or the “seat of the soul”, located at the frontal center of the brain, between the crevice where the two halves of the thalamus join, the pineal gland is responsible for sensing light (or, lack thereof) and secreting melatonin in response (Aulinas, 2019). As a result, the pineal gland regulates sleep-wake cycles, circadian rhythm, cell protection, and neuroprotection (Aulinas, 2019). Recently, researchers noted physiological abnormalities in the pineal gland among individuals with schizophrenia. This finding suggests that the pineal gland volume and function may have a role in development of the disease and associated symptoms.

It is crucial that health care providers continue advocate for better understanding of schizophrenia, in order to develop a more appropriate treatment. Current first line treatments for

individuals with schizophrenia are primarily pharmacologic in nature. The development of Chlorpromazine (Thorazine) in 1952, proved to be revolutionary for treatment of schizophrenia and other types of mental illness. Prior to the development of this medication, individuals with schizophrenia most often were institutionalized and sometimes treated through electroshock therapy (Patel, 2014). Since then, other pharmacologic agents have been developed, and these continue to be a paramount source of treatment for individuals with schizophrenia.

Without a clear understanding of the cause of the disease, health care providers are only able to treat the symptoms of schizophrenia. However, psychotropic pharmacologic agents are not without side effects: weight gain, sedation, seizures, and movement disorder such as tardive dyskinesia are unfortunately common (Kane, 2010). Alternative therapies, particularly those involving the pineal gland and melatonin, should be further explored. More research is needed into the pineal gland and its potential to demystify the disease process present in schizophrenia.

Problem statement

What is the relationship between pineal gland physiologic function and development of schizophrenia?

Purpose

The purpose of this thesis is to critique the literature focusing on the role of melatonin and pineal gland abnormalities in the development and symptoms severity of schizophrenia.

Literature Review

As previously noted, schizophrenia is not a specific disease. Rather, this diagnosis includes a range of symptoms and behaviors; often classified as “positive” or “negative”. Positive symptoms refer to “extra” behaviors or experiences that manifest in the form of delusions, flight of ideas, ambivalence, bizarre behavior, loose associations, echopraxia, hallucinations, preservation, and ideas of reference. On the other hand, negative symptoms refer to impaired emotion or affect. Examples of negative symptoms include alogia, anhedonia, apathy, asociality, blunted affect, catatonia, flat affect, avolition, and inattention (Sarkar, 2015).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for schizophrenia requires the presence of two or more of the following symptoms, present for at least on month:

- Delusions
- Hallucinations
- Disorganized speech (e.g., frequent derailment or incoherence)
- Grossly disorganized or catatonic behavior
- Negative symptoms (i.e., diminished emotional or avolition).

Of these 5 symptoms, one of the two must be delusions, hallucinations or disorganized speech in order to warrant a schizophrenia diagnosis (Substance Abuse and Mental Health Services Administration, 2016). Nurses should be aware that individuals with schizophrenia are at risk for disturbed thought process and self-care deficit, and plan care accordingly. To understand the potential role of the pineal gland and its role in schizophrenia, theories on

schizophrenia, pineal gland function, current treatments, and pineal abnormalities must first be explored.

Theories associated with development of Schizophrenia

In the past, the etiology of schizophrenia was hypothesized to have social and interpersonal origins, however, the more prevalent current school of thought focuses largely on the biologic factors at play. Evidence supporting the argument for biologic causes has proven to be more frequent and widely accepted then its sociologic counterpart. Presently, genetics, viruses, and neuroanatomy or neurochemicals disturbances are hypothesized to be the three predominant causes of schizophrenia (Videbeck, 2019). Current genetic theories suggest that schizophrenia is a polygenetic trait, meaning that multiple genes attribute to the development of the disorder. This theory is supported by studies conducted in families, particularly with identical twins. When one identical twin has schizophrenia, the other twin has a 50% chance of developing the disorder. On the other hand, fraternal twins only present a 15% risk of developing this condition (Videbeck, 2019). If the etiology of schizophrenia related to only one gene, both identical twins would develop schizophrenia. To date, genetic research focusing on schizophrenia has not identified a particular gene or genes that are responsible for the disorder.

Another theory focusing on the biologic etiology of schizophrenia relates to immunovirology- that is, the body's response to a virus. The immunovirology theory attributes the development of schizophrenia to childhood or prenatal exposure to certain viruses. This theory is supported by the rise in schizophrenia cases a generation after waves of flu affected England in the mid-1900s (Brown & Derkits, 2010). Additionally, the role of cytokines in

infection and mental health have been brought to question. The key role of cytokines is to mediate inflammatory and immune responses. However, cytokines have a lesser known function, that is, behavior and neurochemical modulation. The theory of immunovirology hypothesizes that exposure to viruses and the reaction of cytokines results in changes to behavior and neurochemistry

Neuroanatomy and neurochemical disturbances also pose a potential cause of schizophrenia. As if a culmination of multiple theories, the neuroanatomy theory observes that individuals with schizophrenia have differences in brain structure compared with those without schizophrenia. These anatomic differences include less cerebral spinal fluid and brain tissues in affected individuals, as well as larger ventricles and diminished glucose and oxygen metabolism (Skudlarski, 2010). Neurochemical differences include excess production of dopamine and serotonin. An excess of dopamine is a commonly cited immediate cause for the symptoms of schizophrenia. The influence of melatonin, regulated by the pineal gland, will be discussed further in this thesis. Research on the pineal gland warrants further discussion on a potential biologic factor associated with schizophrenia, particularly the theory of neuroanatomy.

A rising star: The pineal gland and melatonin

The understand the role of the pineal gland in schizophrenia, the role of this gland in a neurotypical brain must be examined. The pineal gland, located between the two hemispheres of the brain, is best known for its role in melatonin secretion, and regulation of the circadian rhythm. Melatonin, a derivative of serotonin, is secreted relative to the amount of light detected by the retinas of the eye. In a well-functioning pineal gland, exposure to light will decrease the

secretion of melatonin by the pineal gland, resulting in wakefulness (Aulinas, 2019). Conversely, a lack of light, such as during evening time, will promote secretion of melatonin, resulting in drowsiness. While the role of melatonin and the sleep-wake cycle should not be understated, the melatonin and the pineal gland affect a variety other system as well. Melatonin is related to memory, growth hormone secretion, ovarian physiology, and osteoblast differentiation (Aulinas, 2019). The unique properties of melatonin include antinociception, antidepression, anxiolytic, locomotor activity-regulating, neuroprotective, anti-inflammatory, pain-modulating, along with blood pressure-reducing, retinal, vascular, anti-tumor, and antioxidant effects (Emet, 2016).

The systemic effect of melatonin can be partially attributed to the widespread prevalence of melatonin receptors in the body. Melatonin receptors can be found in the brain, retina, cardiovascular system, cardiac ventricular wall, aorta, coronary and cerebral arteries, liver and gallbladder, duodenal enterocytes, colon, cecum and appendix vermiformis, skin, parotid gland, exocrine pancreas, kidney, cells of immune system, platelets, brown and white adipocytes, epithelial cells of prostate and breast, ovary/granulosa cells, myometrium, placenta and fetal kidney (Emet, 2016). One reason melatonin is more widely researched is associated with its unique property to pass through the blood brain barrier and accumulate in the central nervous system at a rate higher than most neurochemicals (Andrabi, 2019). As a result, melatonin can produce strong neurochemical affects. Perhaps most key to schizophrenia is melatonin's dopamine inhibiting properties. Previous studies have explored the role of melatonin and dopamine inhibition in the context of Alzheimer's, Parkinson's, and strokes, and the findings are promising for melatonin's role in schizophrenia. Consequently, the role of melatonin and the pineal gland on dopaminergic system is of key importance.

Current treatment

As previously discussed, modern treatment of schizophrenia relies heavily on pharmacologic interventions. Specifically, symptom management of schizophrenia is achieved through first- and second-generation antipsychotic medications. First generation antipsychotic mediations work well to reduce the positive signs of schizophrenia such as hallucinations, disturbed thinking, and delusions. The first-generation medication are dopamine agonists, and work by inhibiting blocking the D2, D3, and D4 receptors of the neurotransmitter dopamine (Kane, 2010). Second generation antipsychotics work by blocking the receptors of both dopamine and serotonin. The effect on serotonin enables second generation antipsychotic to manage both the positive and negative signs of schizophrenia. Some antipsychotics can be given in injections to combat the skipping or misuse of medication by individuals with schizophrenia. The paramount dilemma with administering antipsychotic medication is the side effects. For antipsychotics, extrapyramidal side effects are of particular concern. Extrapyramidal (EPS) side effects refers to a collection of neurologic symptoms that occur due to the blockage of the D2 receptor in the brain stem (Weng, 2019).

Among others, EPS can include, among others, acute dystonia, tardive dyskinesia, neuroleptic malignant syndrome, psuedoparkinsonisms, and akathisia. Additional side effects include metabolic syndrome, decreased libido, and an increased risk for breast cancer (Weng, 2019). Another downside to associated with psychopharmacology side effects serve as barriers, to individuals with schizophrenia adhering to their recommended treatment regimen. Adherence barriers may be associated with socioeconomic factors, such as an inability to pay for the medicine, or lack of transportation to obtain medicine. Medication nonadherence often is

attributed to unpleasant side effects, difficulty adhering to a schedule, belief that the individual "doesn't need" the medication or feels worse while being on the medication. While psychotropic pharmacology has been incredibly beneficial to the management of schizophrenia, understanding the role of the pineal gland in schizophrenia might enable providers to treat the disorder more effectively with fewer negative side effects.

Changes to the pineal gland

Changes to the pineal gland lead to subsequent alteration to the systems that are influenced by the gland. Possible alteration to the pineal gland my occurs due to a variety of factors such as smoking, inadequate in utero nutrition, or obesity along with environmental exposures such as fluorides, tobacco, and some food additives (Takahashi, 2019).

Several studies investigated anatomic differences in the pineal glands of individuals with schizophrenia. The most frequent abnormality observed was a decrease pineal volume in those with schizophrenia (Takahashi, 2019). However, results have not been consistent (Aulinas, 2019). For example, early studies of pineal volume in individuals with schizophrenia found no abnormalities, but more recent literature attributes decreased pineal volume to early neurobiological alterations. The current literature, however, suggests that pineal gland volume does not change over time in affected individuals (Takahashi, 2019). Hence, individuals with chronic schizophrenia maintain pineal volume despite living with the disorder for a longer time. Similarly, pineal volume did not change with dose or duration of antipsychotic medication (Takahashi, 2019). These findings indicate decreased pineal volume could be a risk factor for development of schizophrenia, rather than a cause of the disease. However, it should also be

noted that behaviors that lead to pineal abnormalities parallel risk factors for development of schizophrenia (ex. Smoking, poor nutrition, obesity).

Lack of correlation between pineal volume and severity of symptoms further supports the theory that the pineal gland has not yet been found to be a convincing risk of developing schizophrenia. Perhaps more promising is the role of melatonin in affected individuals. In a study by Morera-Fumero, decreased serum melatonin levels were found to be correlated with conceptual disorganization (Morera-Fumero, 2011). Reports of diminished melatonin levels in affected individuals is supported by an identical twin study. Afonso found that in the affected twin, nighttime melatonin secretion was significantly lower than his healthy counterpart. As a result, the affected twin experienced prolonged periods of restlessness and impaired quality of sleep (Afonso, 2010). Research into melatonin as treatment for schizophrenia is promising, but strong evidence is lacking at this time.

Alternative treatments and links to melatonin

Current nonpharmacological alternative treatments center primarily around melatonin production and dietary changes. The treatment most pertinent to pineal gland involvement is melatonin. In a study conducted on rats, melatonin was able to reduce the histological changes caused by injection of MK-801 (Andrabi, 2019). MK-801, or Dizocilpine more specifically, is a NMDA receptor antagonists which among other things, creates schizophrenia-like symptoms in lab rats. The use of melatonin in diminishing these symptoms indicates that melatonin may be useful in managing schizophrenia symptoms in affected humans. Aside from symptom treatment, melatonin has been found to decrease the side effect of weight gain associated with the

antipsychotic drug olanzapine. In a 2014 study by Modabbernia (N= 48), an 8 week treatment of melatonin correlated with a 3.2 kg difference in weight gain, decreases waist circumference, and triglyceride concentration (Modabbernia, 2014).

Other alternative theories for symptom management focus on dietary changes and incorporating nutritional supplements. Of particular interest is the ketogenic diet and incorporating vitamin d and folic acid supplements. Dietary modifications are of interest related to the melatonin level in the body. Production of melatonin relies on availability of its precursor, tryptophan. If amino acids are restricted in the diet, it may lead to a decrease in tryptophan and a consequential decrease in melatonin (Peuhkuri, 2012). Additionally, low levels of zinc, folate, and magnesium have been linked to lower levels of melatonin (Peuhkuri, 2012). Current research continues to find evidence that melatonin has promise for aiding in management of schizophrenia. Therefore, it is beneficial to understand dietary changes effect on melatonin, and how melatonin supplements may be used alongside pharmacological and life style interventions.

Conclusion

Schizophrenia is a complicated and poorly understood psychiatric disorder. Recent pharmacological advancements have made it possible for affected individuals to manage symptoms. However, there are significant side effects associated with current antipsychotics. Some correlation has been found between a decreased pineal volume, and risk for development of schizophrenia. The use of melatonin has been supported to be effective for decreasing both symptoms of schizophrenia and decreasing side effects associated with antipsychotic

medications. Further research into the pineal gland and its effect on neurobiology yields promise for deepening understanding of schizophrenia.

Methodology

A review of published literature focusing on the pineal glands association with schizophrenia was performed using several databases including: ScienceDirect, PubMED, Google Scholar, Cumulated Index to Nursing and Allied Health Literature (CINAHL), and Elton B. Stephens Co. (EBESCO). Key search terms included: Pineal gland, melatonin and schizophrenia, pineal gland and schizophrenia, sleep and schizophrenia, melatonin and treatment for schizophrenia, alternative treatments for schizophrenia, and pineal volume and schizophrenia. Inclusion criteria will include research published from 1998-2020. Exclusion criteria will include research published not in the English language, research outside of the specified published date, or research not relevant to the topic. (See Appendix A Figure 1: Methodology Consort Chart)

An evidence table was developed to summarize the articles critiqued by the researcher and included in the appendices. Each research article was analyzed, critiqued, synthesized, and extracted by the researcher. Consistent and inconsistent findings along with gaps in the literature will be discussed.

Discussion

Throughout the literature, there have been various discussions about the pineal gland, melatonin, and schizophrenia. The results indicate that while pineal gland abnormalities are often present in schizophrenia, there is not yet strong evidence to suggest that these abnormalities are causative factors in the development of schizophrenia. The literature indicates that severity in pineal abnormalities are not linked to severity in clinical presentation of the disorder. Discussion of melatonin in relation to schizophrenia consistently found lower serum melatonin levels in affected individuals. Individuals with schizophrenia present largely with disrupted circadian rhythms, linked possibly to decreased serum melatonin levels, however the literature is not conclusive in terms of exact cause for these disruptions. Melatonin supplements have been shown to decrease the severity of some clinical presentations of schizophrenia, however, research on the subject is still limited.

Inconsistent findings include discussion of the severity of symptom reduction in individuals with schizophrenia given melatonin, and which symptoms showed improvements. Melatonin's link to increased sleep efficiency cannot be overlooked. Inconsistent findings could be related to the remedying of sleep deprivation and insomnia in affected individuals, and the various responses to these strenuous circumstances.

More research is needed to isolate the efficacy of melatonin on specific populations in varying environments. Gaps in the literature include the relationship between serotonin and melatonin, the effectiveness of melatonin in outpatient vs inpatient settings, the effectiveness of

melatonin on various skin pigments, ages, and sexes, and the relationship between physical pineal abnormalities and their relation to melatonin production.

Implications for nursing

The next section highlights implications for nursing policy, education, practice, and research. Limitations of this review are highlighted.

Policy

Policies such as 3rd party payers providing expanded coverage for medications and services provided by advanced practice nurses focusing on individuals diagnosed with schizophrenia has made improvements to the quality of life of the affected population and their caregivers, however, there are still reimbursement policies to be made. To start, community based mental health services require increased funding. Funding for mental health resources is sources primarily from the federal or state level and in some cases local tax initiatives. While large financial investments are dedicated to mental health services, the percentage of the population who are utilizing such services does not correlate. For example, Florida spends over 700 million dollars on State Mental Health Agency Expenditures annually, but less than 2% of the Florida population utilizes these services (National Rehabs Directory, 2019). This ratio highlights another necessary policy change: programs that promote accessibility of services. One of the many systemic factors that prevent individuals with schizophrenia from seeking or following up with care is the lack of accessibility associated with transportation, location, or financial constraints (Wood, 2014). Many individuals with schizophrenia also have dual diagnoses such as substance abuse, homelessness, or veteran status, which pose additional barriers to care. Policy changes to improve accessibility of care may include improving public transportation through adequate funding, as well as greater involvement of state sanctioned

guardians in follow up care for those with a diagnosis of schizophrenia. There is much to be done in the way of policy changes to support individuals with schizophrenia, but fiscal support for community-based programs and more user-friendly transportation would help bridge some of the gaps where inaccessibility to care thrives.

Education

The educational workload surround schizophrenia lies mostly in public destigmatization of the disorder. Although greater awareness for the disorder has led to improved public perceptions, stigma remains as one of the greatest challenges to those with a schizophrenia diagnosis. In a 2008 study that surveyed 1070 individuals from the English public about their attitudes towards mental illnesses, in the study, 63% of participants believed those with schizophrenia to be a danger to others, 54% reported believing that those affected "feel different from us", and 50% labeled those with schizophrenia as hard to talk to (Wood, 2014). Public programs aimed at reducing stigma have been somewhat successful in the past. In a five-year campaign (1998) entitled 'Changing Minds : Every Family in the Land' had some success in altering public attitudes regarding individuals with schizophrenia (Crisp, 2000). Objectives for public education should center around highlighting statistics that support perception of individuals with schizophrenia as more of a threat to themselves than others, health disparities faced by those with a schizophrenia diagnosis, information on local resources, and teachings regarding how to handle an individual experiencing psychosis in a safe and helpful manner. Similar objectives would be beneficial if integrated into psych or advanced practice nurse practitioner curricula. Table 2: Teaching Proposal illustrates an example of a teaching proposal that would be appropriate for a community outreach education session.

Nursing practice

Implications for nursing practice include increased use of alternative therapies for symptom management such as melatonin supplements and sunlight exposure. Melatonin supplements have been shown to reduce symptom severity in individuals with schizophrenia. A 2007 study found that 3mg of melatonin administered to schizophrenic patients suffering from insomnia improved the quality and depth of nighttime sleep, reduced the number of nighttime awakenings, and increased the duration of sleep without producing a morning hangover. Subjects also reported elevated mood and improved daytime functioning the morning after receiving the dose of melatonin (Suresh, 2017). Sunlight exposure has been documented to effect mood and exacerbate or alleviate psychiatric symptoms. The most obvious correlation between decreased sun exposure and declines in mental health is found in Seasonal Affective Disorder. Additionally, incidences of psychosis increased during times of the year of decreased sunlight (Gu, 2019). The positive feedback loop between sunlight exposure and melatonin regulation makes a strong argument for increase sunlight exposure to both manage psychosis and encourage melatonin production.

Research

Information surround schizophrenia etiology and treatment is consistently growing and changing and there is limited nursing research focusing on level of melatonin and schizophrenia . Further nursing research is needed regarding the effect of neonatal sunlight exposure, the role of the pineal gland and serotonin in melatonin production, variations in melatonin production on differing skin pigment and genders.

Limitations

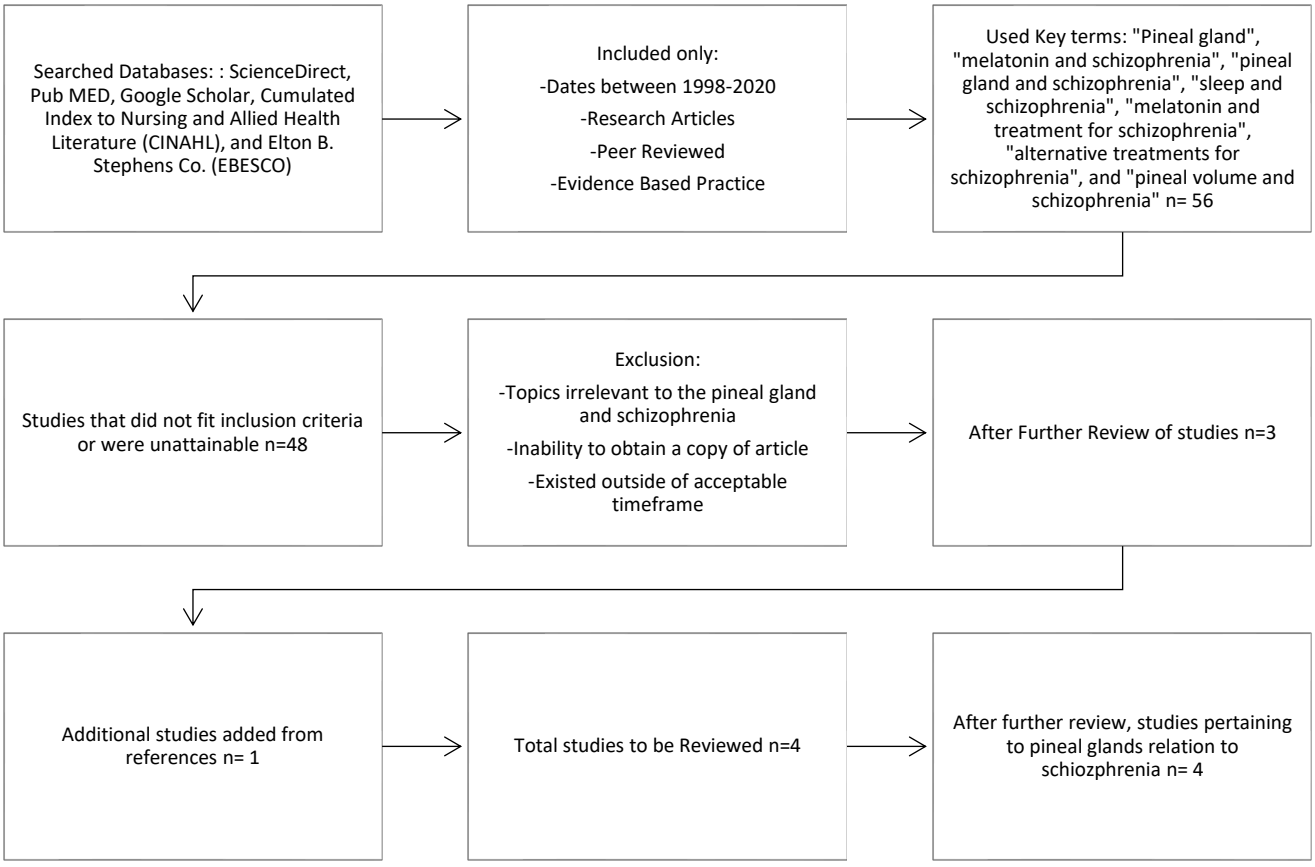
Several limitations are noted for this integrative review of the literature, including only studies published in the English language from 1998 To 2021. There tends to be more available information in the alternative media on the pineal gland and melatonin relative to schizophrenia symptoms and management.

Summary

In summary, this integrative review of the literature focusing on the relationship between pineal gland abnormalities and melatonin production found no significant correlation between pineal abnormalities and symptom severity in individuals diagnosed with schizophrenia. Use of alternative therapies such as melatonin show promise in decreasing symptom severity in those with a schizophrenia diagnosis. More research is needed into relationship between serotonin and melatonin, the effectiveness of melatonin in outpatient vs inpatient settings, the effectiveness of melatonin on various skin pigments, ages, and sexes, and the relationship between physical pineal abnormalities and their relation to melatonin production.

Appendices A

Figure 1: Methodology Consort Chart


Searched Databases: : ScienceDirect, Pub MED, Google Scholar, Cumulated Index to Nursing and Allied Health Literature (CINAHL), and Elton B. Stephens Co. (EBESCO)
Included only:
-Dates between 1998-2020
-Research Articles
-Peer Reviewed
-Evidence Based Practice
Used Key terms: "Pineal gland", "melatonin and schizophrenia", "pineal gland and schizophrenia", "sleep and schizophrenia", "melatonin and treatment for schizophrenia", "alternative treatments for schizophrenia", and "pineal volume and schizophrenia" n= 56
Studies that did not fit inclusion criteria or were unattainable n=48
Exclusion:
-Topics irrelevant to the pineal gland and schizophrenia
-Inability to obtain a copy of article
-Existed outside of acceptable timeframe
After Further Review of studies n=3
Additional studies added from references n= 1
Total studies to be Reviewed n=4
After further review, studies pertaining to pineal glands relation to schiozphrenia n= 4

Appendices B

Table 1: Table of Evidence

Citation	Study design and purpose	Sample size	Relevant Findings	Limitations	Was a relationship found between pineal gland or melatonin abnormalities and schizophrenia development or symptoms severity? 1= yes 2=no 3=inconclusive 4= not applicable/not tested	Did compensating for abnormalities improve symptoms? 1= yes 2=no 3=inconclusive 4=not applicable
(Afonso, 2010)	present the findings of wrist actigraphy and salivary melatonin profiles in a patient with schizophrenia and his homozygotic healthy twin.	2	The affected twin presented lower melatonin production and low-threshold dim-light melatonin onset (DLMO < 3 pg/mL) as compared to the non-affected twin, who presented the normal nocturnal rise	Limitations exist concerning collection of salivary melatonin. Since activity and postural changes could affect the concentration of circulation melatonin, in this study the subjects were recommending staying sitting during the sampling period; however, our patient was in remission, and his family supervised the salivary collections. Self-report questionnaires like the PSQI	1	3

				are limited by patients' low insight, and probably low expectations regarding sleep; other instruments could have produced larger differences between the twins in this aspect. Volumetric MRI of the twins' pineal glands could have shown differences in structure that might explain the discrepant melatonin levels. Finally, our results must be viewed with caution due to comparing only two individuals.		
(Andrabi, 2019)	to assess the potential of melatonin in attenuating MK-801 induced schizophrenia-like behavioral and brain neurotoxicity markers.	6	Our data demonstrated that the treatment with melatonin attenuates the schizophrenic like symptoms in the mice having a protective effect on prefrontal cortex region of brain by mitigating the alteration of neurotoxicity markers. The protective effect of the treatment was shown to reduced elevation of AChE, *c*-fos expression and histopathological alterations.	Small sample size	1	1

(Morera-Fumero, 2011)	The aim of this research is to study whether serum melatonin level is related with positive psychopathology in a sample of paranoid schizophrenia patients.	32	The only significant correlation, with a positive sign, was the item Conceptual Disorganisation (P2) with serum melatonin at 24:00 h ($r = 0.355$, $p < 0.046$).	None stated	3	4
Shamir, 2000	measured melatonin output in patients with chronic schizophrenia and assessed the effects of melatonin replacement on their sleep quality.	19	All patients had low melatonin output. Melatonin replacement significantly improved rest-derived sleep efficiency compared with placebo (83.5% vs. 78.2%, $p = .038$) in this population. Improvement of sleep efficiency was significantly greater ($p < .0014$) in low-efficiency (80% vs. 67%) than high-efficiency sleepers (88% vs. 90%). In addition, during melatonin therapy, tendencies toward shortened sleep latency (by 40 minutes, $p < .056$) and increased sleep duration (by 45 minutes, $p < .078$) were observed in low- but not high-efficiency sleepers.	None stated	4	1

Takahashi, 2019	In this study, magnetic resonance imaging (MRI) was performed to measure the pineal gland volume in patients with schizotypal disorder and the results were compared with data obtained in patients with schizophrenia and healthy controls.	246	The present study demonstrated similar reduction of pineal volume in a relatively large group of patients with schizotypal disorder and schizophrenia. We found no significant relation between morphologic features of the pineal gland (such as its volume and cystic change) and clinical variables in either patient group. While we were unable to directly assess the mechanism underlying changes of pineal volume, low melatonin levels in utero and/or during early life may influence neurodevelopment by inhibiting neuronal differentiation and axogenesis (Galván-Arrieta et al., 2017). It was also reported that the pineal volume normally increases during infancy, and then remains stable (Sumida et al., 1996). Taken together with our previous finding of a stable pineal volume in various stages of schizophrenia (Takahashi et al., 2019), it is possible that the pineal volume indicates a common vulnerability to neurodevelopmental pathology in schizophrenia spectrum disorders	None stated	3	4

(Onaolapo, 2017)	The aim of this study was to assess the potentials of oral melatonin supplement in the management of induced schizophrenia-like behavioral and brain oxidative status changes, using an animal model.	60	The results of this study revealed that melatonin supplementation was associated with: 1) a reversal of ketamine-induced social-interaction deficits, 2) decrease in ketamine-induced hyperlocomotion (horizontal locomotion and rearing) and self-grooming behaviours 3) reversal of ketamine-induced memory-deterioration 4) reversal of ketamine-induced changes in brain antioxidant activity. Also, at the doses administered, melatonin's overall ability to counteract ketamine-induced behavioural changes was better than haloperidol and comparable to olanzapine; while its ability to counteract brain oxidative stress was a significant improvement over olanzapine and haloperidol.	None stated	4	3

Appendices 3

Table 2: Teaching Proposal

Objectives	Timeline	Implementation/Outline	Evaluation Plan
Individuals will be able to identify key factors about schizophrenia that lead to decreased quality of life for the affected individuals.	By the end of the session	This objective will be met through a verbal presentation coupled with a PowerPoint and showing of videos involving firsthand accounts of what it is like to live with schizophrenia.	Individuals will be able to verbalize key factors about schizophrenia that lead to decreased quality of life for the affected individuals.
Individuals will be able to identify health disparities faced by those with schizophrenia and relate these disparities to systemic causes.	By the end of the session	This objective will be met though presentation of statistic related to health care exposure in the schizophrenic community.	Individuals will be able to verbalize health disparities faced by those with schizophrenia and relate these disparities to systemic causes.
Individuals will be able to demonstrate an understanding of therapeutic communication and de-escalation as it relates to individuals experiencing psychosis.	By the end of the session	This objective will be met through enlisting qualified healthcare professionals to demonstrate proper execution of these techniques.	Individuals will be able to demonstrate an understanding of therapeutic communication and de-escalation as it relates to individuals experiencing psychosis.

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