BRAIN. Broad Research in Artificial Intelligence and Neuroscience
ISSN: 2068-0473 | e-ISSN: 2067-3957
Covered in: Web of Science (WOS); PubMed.gov; IndexCopernicus; The Linguist List; Google Academic; Ulrichs; getCITED; Genamics JournalSeek; J-Gate; SHERPA/RoMEO; Dayang Journal System; Public Knowledge Project; BIUM; NewJour; ArticleReach Direct; Link+; CSB; CiteSeerX; Socolar; KVK; WorldCat; CrossRef; Ideas RePeC; Econpapers; Socionet.

2022, Volume 13, Issue 1Sup1, pages: 175-187 | https://doi.org/10.18662/brain/13.1Sup1/311
Submitted: February 1st, 2022 | *Accepted for publication:* March 4th, 2022

Evaluation Of the Salivary Flow in Patients with Schizophrenia. A Literature Review

Ionuţ TĂRĂBOANŢĂ[1], Andra Claudia TĂRĂBOANȚĂ-GAMEN[2], Stefan Lucian BURLEA[3], Liliana LUCA[4], Angela Cristina GHIORGHE[5], Sorin ANDRIAN[6]

[1] Assistant professor, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania, ionut-taraboanta@umfias.ro
[2] Assistant professor, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania, andra.gamen@gmail.com
[3] Associate Professor, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania, lucianburlea@yahoo.com
[4] PhD student, "Dunărea de Jos" University, Galaţi, Romania, chiroscaliliana@gmail.com
[5] Associate professor, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania, drangycris@yahoo.com
[6] Professor, "Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania, sorinandrian@yahoo.com

Abstract: *Schizophrenia is a chronic psychiatric disease that affects approximately 1% of the global population. Schizophrenia is characterised by positive, negative and cognitive symptoms. The etiological factors of this psychiatric illness are not fully deciphered, but the most incriminated are genetic factors and environmental risk factors.*
The treatment of schizophrenia has the role of reduction the duration and intensity of episodes and consists in the administration of typical or atypical antipsychotic drugs, antiparkinsonian, anxiolytic, sedatives or antidepressants. Of these, some of the drugs may have side effects that modify patients' salivary flow rates.
Xerostomy is a subjective sign characterized by a dry mouth sensation and is caused by hypofunction of the salivary glands. According to a series of studies, xerostomia can be an adverse effect of typical antipsychotic medication as well as antiparkinsonian medication. Sialorrhea is caused by hyperfunction of the salivary glands and is characterized by an increased secretion of saliva. This side effect is especially noticeable during the night sleep. Alteration of salivary function creates increased discomfort to the schizophrenic patient, which causes him to give up regular medication.
The aim of this study is to review the literature on the link between schizophrenia, the treatment of schizophrenia and impaired salivary function.

Keywords: *Schizophrenia, Saliva, Xerostomia, Antiphychotic, Salivary flow rate.*

How to cite: Dumea, E., Efrim, N.D., Petcu, A., Anghel, L., & Puscasu, C.G. (2022). Evaluation Of the Salivary Flow in Patients with Schizophrenia. A Literature Review. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience, 13*(1Sup1), 175-187. https://doi.org/10.18662/brain/13.1Sup1/311

1. Introduction

Schizophrenia is one of the most frequent mental disorders with a global prevalence of 1% (Coulon et al., 2016; Moś, 2015). It is characterised by positive symptoms (Coulon et al., 2016), like hallucinations (false perceptions) and delusions (false beliefs) and negative symptoms, like apathy, or diminshed expression of affection (Moś, 2015). The etiology of this illness has not been completely discovered, however, two factors are incriminated in the literature: the genetic basis and the association with environmental risk factors (Tandon et al., 2008).

The treatment of schizophrenia consists mostly of psychotropic drugs (antipsycholitics, antidepressants or mood stabilizers) (Moś, 2015) with a major impact on oral health (Rosa et al., 2021). Some studies have reported that oral side effects (like hypo- or hypersalivation) of drugs used in the treatment of schizophrenia represent a factor that causes patients to give up these drugs (Mohandoss & Thavarajah, 2019).

Saliva has a very important role in maintaining an optimal oral status, and its quantitative variations may be accompanied by oral conditions such as xerostomia (dry mouth sensation), carious lesions, or periodontal disease (Krunić et al., 2013). On the other hand, psychiatric patients represent a risk group for oral disorders, both because of psychotropic medication side effects and as a result of the minimal attention they pay to oral hygiene, or increased consumption of alcohol and cigarettes (Velasco-Ortega et al., 2019).

The aim of this is to conduct a literature review on the connection between schizophrenia, the treatment of schizophrenia and the changes of the salivary flow rate.

2. Schizophrenia

2.1 Etiology

2.1.1. Genetic bases

The etiological factors incriminated in the occurrence of schizophrenia have not been completely deciphered, so there are several theories that describe this disorder as the result of the interaction between genetic, psychological and environmental risk factors (Đorđević et al., 2016).

Over time, a number of studies have succeeded in demonstrating the genetic basis of schizophrenia, analyzing the incidence of this psychiatric disorder in families where one of the members had been diagnosed with

schizophrenia (Kendler et al., 1993). Other authors drew these conclusions by comparing the number of schizophrenic patients with biological parents diagnosed with schizophrenia, to the number of patients with adoptive parents diagnosed with schizophrenia. Therefore, the results of this research demonstrated the genetic transmission of this psychiatric disorder (Shore, 1993).

Research on twins has shown that dizygotic twins share 50% of the genetic material, while monozygotic twins share 100% of the genetic material (Chirita et al., 2012). Therefore, if a dizygotic twin suffers from this disease, the risk of schizophrenia of the other twin is about 15-20%, while in the case of monozygotic twins, the risk is 40-50% (Tandon et al., 2008; Untu et al., 2015). Schizophrenia is described as a heterogeneous, multifactorial or polygenic disorder with a wide variety of genetic polymorphisms (Đorđević et al., 2016; Tandon et al., 2008).

2.1.2. Environmental risk factors

Environmental risk factors counted in biological and psychosocial factors with which the patient interacted in the prenatal, postnatal, childhood or adolescence period (Tandon et al., 2008).

In the prenatal period, the main risk factors incriminated in the development of schizophrenia are determined by maternal infections, of which the most common are influenza infection, rubella or toxoplasmosis (Sjögren & Nordström, 2000).

Other risk factors encountered in the prenatal period are represented by complications at birth, where the most common is fetal hypoxia (Cockburn et al., 2017).

A series of studies bring into question a very interesting factor, but without any scientific explanation, namely the period of birth. A 5-10% increase in the risk of developing schizophrenia has been reported in patients born in late winter or early spring (Ciobotea et al., 2016; Habtewold et al., 2020).

During childhood, the risk factors associated with the development of this psychiatric disorder are mainly represented by mental traumas, such as parental separation, infections, or head injuries (Ciubara et al., 2015; Tandon et al., 2008).

During adolescence, the incriminated factors are represented by stress or events with increased emotional involvement. Another risk factor in the development of schizophrenia is high drug consumption, such as cannabis (Shah et al., 2012).

2.2. Symptoms

Schizophrenia has three main categories of symptoms:

Positive symptoms: hallucinations, paranoia, exaggerated or distorted perceptions, beliefs, behaviors and movement disorders (catatonia, ecopraxia, ecomimia, psychomotor agitation)

Negative symptoms: emotional blunting, avolition (lack of motivation), alogia (decreased rhythm and flow of spontaneous speech; may reflect impoverishment of thought), anhedonia (diminished or lack of ability to feel pleasure), attention deficit, social withdrawal (Buchanan, 2007; Radulescu et al., 2020).

Cognitive symptoms: confused and disordered thinking and speech, logical reasoning deficits (Habtewold et al., 2020).

2.3. Treatment of schizophrenia

The objectives of the treatment are:

- decrease the duration and the intensity of the psychotic. episodes.
- diminish mortality.
- improve adaptation to social life (Đorđević et al., 2016).

The treatment of schizophrenia consists principally of antipsychotics of first generation (also known as traditional or typical) or second generation (atypical), antidepressants, anxiolytics, or antiparkinsonians (Đorđević et al., 2016; Moś, 2015). The therapeutic effect of the first generation antipsychotics consists of an antagonistic reaction on dopamine D2 receptors, while the effect of the second generation antipsychotics is based on an antagonism on serotonin A2 receptors (Bertaud-Gounot et al., 2013; Đorđević et al., 2016).

The most commonly used first-generation antipsychotics are chlorpromazine, haloperidol, sulpiride, levomepromazine. Over time a number of side effects have been described, the strongest of which are extrapyramidal symptoms, vegetative or neuroendocrine (Krunić et al., 2013; Praharaj et al., 2010). Despite the well-known side effects and the emergence of a new generation of antipsychotics, chlorpromazine remains one of the most widely used drugs for the treatment of schizophrenia, benefiting from its low cost advantage. Xerostomia is a common side effect in patients using these drugs, and this fact can be observed in the oral health of schizophrenic patients treated with chlorpromazine. In situations where the extrapyramidal symptoms are intense, antiparkinsonian drugs can also be used, whose xerostomic effect is associated with that of chlorpromazine (Krunić et al., 2013; Dickerson et al., 2017; Sacuiu et al., 2012).

The second generation antipsychotics currently used in the therapy of schizophrenia, are clozapine, olanzapine, amisulpride or risperidone. This new generation of antipsychotics has recognized as an adverse effect, sialorrhea, increased rate of salivary flow. Clozapine, for example, is an atypical antipsychotic, used in patients with treatment-resistant schizophrenia (Praharaj et al., 2010) and has dual side effects, causing both xerostomia and sialorrhea (in 31-72% of patients) (Mohandoss & Thavarajah, 2019). In patients who used olanzapine, the reported adverse effect was xerostomia (Chaves et al., 2013).

Sialorrhea is an adverse effect that causes the patient a great discomfort, especially because it occurs during night or even during afternoon sleep (Mohandoss & Thavarajah, 2019; Praharaj et al., 2010).

Along with antipsychotics, other drugs are used in the treatment of schizophrenia, in order to reduce side effects, such as antidepressants, antiparkinsonian drugs, anxiolytics or sedatives. These drugs can also cause alterations in the rate of salivary flow, such as xerostomia (Đorđević et al., 2016; Moś, 2015).

3. Salivary flow

Saliva is produced by the parotid, sublingual and submandibular salivary glands in a proportion of 90%, and the remaining 10% is produced by the accessory salivary glands. The parotid glands play a major role in the release of stimulated saliva, and the submandibular glands in the production of unstimulated saliva, while the submandibular glands produce a small amount of stimulated and unstimulated saliva. Mucoid saliva is produced by sympathetic stimulation of the glands, and aqueous saliva is produced by parasympathetic stimulation. Normally, the average quantity of saliva produced in a day is between 0.5 -1.5 l (Rosa et al., 2021).

Saliva is an exocrine, complex biological fluid, composed of 99% water and the rest, proteins, organic and inorganic elements. Therefore, a wide variety of components such as inorganic elements like calcium, magnesium, potassium, sodium, bicarbonate, organic elements such as amylase, peroxidase, polypeptides, glycoproteins, lipases, immunoglobulins, albumins, or other factors with an antimicrobial role can be found in the composition of saliva (Javaid et al., 2016; Rosa et al., 2021).

In the oral environment, saliva has several functions:

- lubrication
- protection of all structures in the oral cavity
- buffer capacity
- clearance

- antibacterial activity
- digestion (Humphrey & Williamson, 2001)

Some studies have shown that between the concentrations of the components present in saliva and those present in the blood, there is a correlation, which is why saliva is used as an object for diagnosing or monitoring general conditions. On the other hand, the main role of saliva is to maintain the homeostasis of the entire oral environment (Liu & Duan, 2012).

The salivary flow can be stimulated when pharmacological agents, mechanical or gustatory stimuli are used to produce saliva, or it may be unstimulated when these techniques are not used (Muddugangadhar et al., 2015). Regarding the salivary flow rate values, there is a great variability, both for stimulated and unstimulated flow. These variations take into account the patient's age, general condition, medication and even the time of saliva sampling, as some studies have shown that there are differences between the rates of daytime and nighttime salivary flow (Humphrey & Williamson, 2001; Muddugangadhar et al., 2015).

Humphrey & Williamson (2001) consider that the normal values of the unstimulated salivary flow must exceed 1 ml /min, and for the stimulated salivary flow, 2 ml /min. The value of unstimulated salivary flow resulted from achieving an average between the flow rate during the waking hours (3ml /min) and the rate of salivary flow during sleep which is close to a value of zero. Regarding the rate of stimulated salivary flow, it is considered to be the main contributor to salivary flow, providing 80-90% of daily saliva secretion (Liu & Duan, 2012).

The lack of the salivary flow leads to the appearance of xerostomia (the sensation of dry mouth) or hyposalivation (the objective decrease of the salivary flow rate) and is associated with subjective symptoms such as oral burning sensation or modified taste perception, or with an increased cariogenic risk (Krunić et al., 2013; Mohandoss & Thavarajah, 2019). Xerostomia alters the quality of life by complicating eating, speaking, or tasting capacity. The decrease of the salivary flow rate is caused by the hypofunction of the salivary glands which is associated to a series of systemic diseases like Sjögren syndrome, or systemic lupus erythematosus, or can be directly connected to drug administration. Previous studies have reported more than 500 drugs that have the side effect of xerostomia, or decreased salivary function (Krunić et al., 2013; Scully, 2003).

On the other hand, the increase in the rate of the salivary flow, or sialorrhea, occurs especially during the night and is associated with the

appearance of halitosis and the sensation of drowning or chocking during sleep (Mohandoss & Thavarajah, 2019; Wolff et al., 2017).

4. Salivary flow in patients with schizophrenia

Studies on the oral health of patients with schizophrenia have shown that they have more severe pathologies compared to the general population, and the dental treatments they receive are limited (Velasco-Ortega et al., 2019).

Schizophrenia associated with its specific medication can alter the rate of salivary flow (Tani et al., 2012; Velasco-Ortega et al., 2019). The modification of the quantity of saliva produced is directly influenced by the type of treatment and the duration of the treatment (Mohandoss & Thavarajah, 2019). The administration of psychotropic drugs for a long period can have adverse consequences on the rate of salivary flow, by decreasing it, due to their adrenergic and anti-alpha-adrenergic effects, blocking parasympathetic stimulation. At the same time, the reduced saliva production can be caused by the damage appeared in the ductal and in the acinar segments of the salivary glands (Tani et al., 2012). In addition, the treatment of schizophrenia based on antipsychotic medication negatively affects the patient's immune system, by altering the oral bacterial microflora (Dickerson et al., 2017). Other side effects of these drugs are the extrapyramidal symptoms, such as dyskinesia or pseudo-Parkinson's disease, which may impair the patient's ability to maintain a proper oral health. On the other hand, the presence of these side effects require the administration of other drugs (such as antiparkinsonians), intended to reduce these symptoms, but also with a negative influence on the rate of salivary flow rate due to their anticholinergic action (Yang et al., 2018). Xerostomy is the main complaint of patients undergoing treatment with antipsychotic medication, and for many of them, it is a reason to give up treatment (Đorđević et al., 2016).

Schizophrenia is a chronic disease, and as a result, treatment is administered over a very long period of time. The main drugs involved in reducing salivary flow are first-generation antipsychotics, such as chlorpromazine, antiparkinsonian or benzodiazepines. To reduce these uncomfortable side effects, patients tend to consume chewing gums, sweets or beverages high in carbohydrates, and this greatly increases their cariogenic risk (Đorđević et al., 2016). Along with the unbalanced diet, another characteristic of the schizophrenic patient is the high rate of cigarette smoking (Persson et al., 2009).

Regarding dental care, the schizophrenic patient rarely visits the dental office for financial reasons, but also out of fear of dental work and neglects his oral hygiene due to cognitive impairments ([a]Lupu et al., 2016; [b]Lupu et al., 2016; [c]Lupu et al., 2016; Moś, 2015).

Chlorpromazine is a first-generation antipsychotic drug, also called typical or traditional, with inhibitory effect on dopamine D2 receptors and muscarinic cholinoceptors. In a study conducted by Krunić et al., (2013) it was observed that the level of unstimulated salivary flow suffered a dose-dependent reduction from a dose of 25 to 175 mg (Navazesh & Kumar, 2008). Chlorpromazine also has neuroendocrine side effects, such as menstrual disorders which are in turn associated with decreased estrogen levels. It has also been shown that estrogen receptors are present in the salivary glands, which is an explanation for the quantitative variations in unstimulated saliva in women with changes in estrogen levels. In conclusion, the reduction of estrogen levels by chlorpromazine also decreases the rate of unstimulated salivary flow (Krunić et al, 2013; Lupu et al., 2015).

Xerostomia is the most common side effect of medication given in schizophrenia, probably due to the increased number of scientific studies, but sialorrhea is also a symptom that the schizophrenic patient encounters, especially those treated with antipsychotics in the second-generation (Mohandoss & Thavarajah, 2019; Rosa et al., 2021).

Clozapine is a second-generation antipsychotic, also called atypical, which acts by an antagonistic effect on alpha-2 adrenergic receptors, reducing laryngeal peristalsis and decreasing the swallowing reflex. Patients treated with clozapine accuse sialorrhea of adverse effects (Garcia et al., 2015).

Normally, in healthy patients, saliva follows a circadian rhythm, where diurnal salivary secretion is increased and nocturnal salivary secretion is decreased. In the schizophrenic patient treated with clozapine, this rhythm is reversed, the nocturnal production being much higher (Praharaj et al., 2010). A number of studies have reported that sialorrhea occurs approximately three weeks after the start of clozapine treatment (Praharaj et al., 2010; Rabinowitz et al., 1996).

5. Conclusion

In conclusion, the rate of salivary flow is altered by the treatment of patients with schizophrenia. Treatment with first-generation antipsychotic medication, alone or in combination with antiparkinsonian medication or benzodiazepines reduces the secretory capacity of the salivary glands.

Multiple studies have shown that second-generation antipsychotic medication has the opposite effect, increasing the rate of salivary secretion, especially at night. Both sialorrhea and xerostomia create a great discomfort for the schizophrenic patient for whom, in many situations, they tend to give up treatment.

References

Bertaud-Gounot, V., Kovess-Masfety, V., Perrus, C., Trohel, G., & Richard, F. (2013). Oral health status and treatment needs among psychiatric inpatients in Rennes, France: a cross-sectional study. *BMC Psychiatry*, *13*(1), 1-9. https://doi.org/10.1186/1471-244X-13-227

Buchanan, R. W. (2007). Persistent negative symptoms in schizophrenia: an overview. *Schizophrenia bulletin*, *33*(4), 1013–1022. https://doi.org/10.1093/schbul/sbl057

Chaves, K. M., Serrano-Blanco, A., Ribeiro, S. B., Soares, L. A., Guerra, G. C., do Socorro Costa Feitosa Alves. M., de Araújo Júnior, R. F., de Paula Soares Rachetti, V., Filgueira Júnior, A., & de Araújo, A. A. (2013). Quality of life and adverse effects of olanzapine versus risperidone therapy in patients with schizophrenia. *Psychiatric Quarterly*, *84*(1), 125-135. https://doi.org/10.1007/s11126-012-9233-3

Chirita, R., Sacuiu, I., Burlea, A., & Chirita, V. (2012). The role of nitric oxide inhibitors in treatment on symptom severity and cognitive deficits in schizophrenia. *International Journal of Neuropsychopharmacology, 15*(Sup1), 113 - 113. https://doi.org/10.1017/S1461145712000508

Ciobotea, D., Vlaicu, B., Ciubara, A., Duica, C. L., Cotocel, C., Antohi, V., & Pirlog, M. C. (2016). Visual Impairment in the Elderly and its Influence on the Quality of Life. *Revista de Cercetare si Interventie Sociala, 54*, 66-74. https://www.rcis.ro/ro/section1/142-volumul-54-2016-septembrie/2293-visual-impairment-in-the-elderly-and-its-influence-on-the-quality-of-life.html

Ciubara, A., Cartas, N., Burlea, L. S., Chirita, R., Ciubara, B. A., Untu, I., & Iliescu, D. B. (2015). The Relationship Between Schizophrenia and Criminality. *European Psychiatry*, *30*(Sup 1), 1-1. https://doi.org/10.1016/S0924-9338(15)30603-9

Cockburn, N., Pradhan, A., Taing, M. W., Kisely, S., & Ford, P. J. (2017). Oral health impacts of medications used to treat mental illness. *Journal of affective disorders*, 223, 184 - 193. https://doi.org/10.1016/j.jad.2017.07.037

Coulon, N., Brailly-Tabard, S., Walter, M., & Tordjman, S. (2016). Altered circadian patterns of salivary cortisol in individuals with schizophrenia: a critical literature review. *Journal of Physiology-Paris, 110*(4), 439 - 447. https://doi.org/10.1016/j.jphysparis.2017.05.002

Dickerson, F., Severance, E., Yolken, R., 2017. The microbiome, immunity, and schizophrenia and bipolar disorder. *Brain, Behavior and Immunity, 62,* 46–52. https://doi.org/10.1016/j.bbi.2016.12.010

Dickerson, B. C., McGinnis, S. M., Xia, C., Price, B. H., Atri, A., Murray, M. E., Mendez, F. M., & Wolk, D. A. (2017). Approach to atypical Alzheimer's disease and case studies of the major subtypes. *CNS spectrums*, *22*(6), 439 - 449. https://doi.org/10.1017/S109285291600047X

Đorđević, V., Dejanović, S. Đ., Janković, L., & Todorović, L. (2016). Schizophrenia and oral health - review of the literature. *Balkan Journal of Dental Medicine*, *20*(1), 15-21. https://doi.org/10.1515/bjdm-2016-0002

Garcia, G. J., Chagas, M. H., Silva, C. H., Machado-de-Sousa, J. P., Crippa, J. A., & Hallak, J. E. (2015). Structural and functional neuroimaging findings associated with the use of clozapine in schizophrenia: a systematic review. *Brazilian Journal of Psychiatry, 37*(1), 71-79. https://doi.org/10.1590/1516-4446-2014-1387

Habtewold, T. D., Rodijk, L. H., Liemburg, E. J., Sidorenkov, G., Boezen, H. M., Bruggeman, R., & Alizadeh, B. Z. (2020). A systematic review and narrative synthesis of data-driven studies in schizophrenia symptoms and cognitive deficits. *Translational psychiatry, 10*(1), 1-24. https://doi.org/10.1038/s41398-020-00919-x

Humphrey, S. P., & Williamson, R. T. (2001). A review of saliva: normal composition, flow, and function. *The Journal of prosthetic dentistry, 85*(2), 162 - 169. https://doi.org/10.1067/mpr.2001.113778

Javaid, M. A., Ahmed, A. S., Durand, R., & Tran, S. D. (2016). Saliva as a diagnostic tool for oral and systemic diseases. *Journal of oral biology and craniofacial research, 6*(1), 67-76. https://doi.org/10.1016/j.jobcr.2015.08.006

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1993). A test of the equal-environment assumption in twin studies of psychiatric illness. *Behavior genetics, 23*(1), 21-27. https://doi.org/10.1007/BF01067551

Krunić, J., Stojanović, N., Ivković, N., & Stojić, D. (2013). Salivary flow rate and decayed, missing, and filled teeth (DMFT) in female patients with schizophrenia on chlorpromazine therapy. *Journal of dental sciences, 8*(4), 418-424. https://doi.org/10.1016/j.jds.2013.05.004

Liu, J., & Duan, Y. (2012). Saliva: a potential media for disease diagnostics and monitoring. *Oral oncology, 48*(7), 569-577. https://doi.org/10.1016/j.oraloncology.2012.01.021

[a]Lupu, V. V., Ignat, A., Paduraru, G., Ciubara, A. M., Ioniuc, I., Ciubara, A. B., Gheonea, C., & Burlea, M. (2016). The study of effects regarding ingestion of corrosive substances in children. *Revista de Chimie*, *67*(12), 2501-2503. https://www.revistadechimie.ro/RCRevChimie.asp?syear=2016&smonth=12

[b]Lupu, V. V., Ignat, A., Ciubotariu, G., Ciubară, A., Moscalu, M., & Burlea, M. (2016). Helicobacter pylori infection and gastroesophageal reflux in children. *Diseases of the Esophagus*, *29*(8), 1007-1012. https://doi.org/10.1111/dote.12429

[c]Lupu, V. V, Ignat, A., Paduraru, G., Ciubara, A., Moscalu, M., Marginean, C. O., & Burlea, M. (2016), Correlation between the different pH-metry scores in gastroesophageal reflux disease in children. *Medicine, 95*(26), e3804. https://doi.org/10.1097/MD.0000000000003804

Lupu, V. V., Ignat, A., Paduraru, G., Mihaila, D., Burlea, M., & Ciubara, A. (2015). Heterotopic Gastric Mucosa in the Distal Part of Esophagus in a Teenager Case Report. *Medicine, 94*(42), e1722. https://doi.org/10.1097/MD.0000000000001722

Mohandoss, A. A., & Thavarajah, R. (2019). Salivary Flow Alteration in Patients Undergoing Treatment for Schizophrenia: Disease-Drug-Target Gene/Protein Association Study for Side-effects. *Journal of oral biology and craniofacial research, 9*(3), 286-293. https://doi.org/10.1016/j.jobcr.2019.06.009

Moś, D. M. (2015). Saliva secretion disorder in a schizophrenic patient-a problem in dental and psychiatric treatment: a case report. *Annals of general psychiatry, 14*(1), 1-5. https://doi.org/10.1186/s12991-015-0052-4

Muddugangadhar, B. C., Sangur, R., Rudraprasad, I. V., Nandeeshwar, D. B., & Kumar, B. D. (2015). A clinical study to compare between resting and stimulated whole salivary flow rate and pH before and after complete denture placement in different age groups. *The Journal of the Indian Prosthodontic Society, 15*(4), 356 - 366. https://doi.org/10.4103/0972-4052.164907

Navazesh, M., & Kumar, S. K. (2008). Measuring salivary flow: challenges and opportunities. *The Journal of the American Dental Association, 139*(Sup. 35S-40S).bhttps://doi.org/10.14219/jada.archive.2008.0353

Persson, K., Axtelius, B., Söderfeldt, B., & Östman, M. (2009). Monitoring oral health and dental attendance in an outpatient psychiatric population. *Journal of Psychiatric and Mental Health Nursing, 16*(3), 263-271. https://doi.org/10.1111/j.1365-2850.2008.01364.x

Praharaj, S. K., Jana, A. K., Goswami, K., Das, P. R., Goyal, N., & Sinha, V. K. (2010). Salivary flow rate in patients with schizophrenia on clozapine. *Clinical neuropharmacology, 33*(4), 176-178. https://doi.org/10.1097/WNF.0b013e3181e204e0

Rabinowitz, T., Frankenburg, F. R., Centorrino, F., & Kando, J. (1996). The effect of clozapine on saliva flow rate: a pilot study. *Biological psychiatry, 40*(11), 1132-1134. https://doi.org/10.1016/S0006-3223(96)89255-9

Rădulescu, I. D., Ciubara, A. B., Moraru, C., Burlea, S. L., & Ciubară, A. . (2020). Evaluating the Impact of Dissociation in Psychiatric Disorders. *BRAIN. Broad Research in Artificial Intelligence and Neuroscience*, *11*(3Sup1), 163-174. https://doi.org/10.18662/brain/11.3Sup1/132

Rosa, L. K., Costa, F. S., Hauagge, C. M., Mobile, R. Z., de Lima, A. A. S., Amaral, C. D., Machado, R. C., Nogueira, A. R. A., Brancher, J. A., & Rodrigues de Araujo, M. (2021). Oral health, organic and inorganic saliva composition of men with Schizophrenia: Case-control study. *Journal of Trace Elements in Medicine and Biology, 66*, 126743. https://doi.org/10.1016/j.jtemb.2021.126743

Sacuiu, I., Chirita, V., Burlea, A., & Chirita, R. (2012). The effect of the atypical antipsychotics on cognitive deficit in schizophrenia. *International Journal of Neuropsychopharmacology, 15* (Sup. 1), 61-61. https://doi.org/10.1017/S1461145712000508

Scully, C. (2003). Drug effects on salivary glands: dry mouth. *Oral diseases*, *9*(4), 165-176. https://doi.org/10.1034/j.1601-0825.2003.03967.x

Shah, V. R., Jain, P., & Patel, N. (2012). Oral health of psychiatric patients: A cross-sectional comparision study. *Dental research journal, 9*(2), 209 - 214. https://doi.org/10.4103/1735-3327.95238

Shore, D., National Institute of Mental Health & Division of Clinical and Treatment Research. (1993). *Special Report: Schizophrenia, 1993 (No. 93).* Schizophrenia Research Branch Sjögren, R., & Nordström, G. (2000). Oral health status of psychiatric patients. *Journal of Clinical Nursing, 9*(4), 632-638. https://doi.org/10.1046/j.1365-2702.2000.00380.x

Tandon, R., Keshavan, M. S., & Nasrallah, H. A. (2008). Schizophrenia,"just the facts" what we know in 2008. 2. Epidemiology and etiology. *Schizophrenia research, 102*(1-3), 1-18. https://doi.org/10.1016/j.schres.2008.04.011

Tani, H., Uchida, H., Suzuki, T., Shibuya, Y., Shimanuki, H., Watanabe, K., ... & Mimura, M. (2012). Dental conditions in inpatients with schizophrenia: A large-scale multi-site survey. *BMC Oral Health, 12*(1), 1-6. https://doi.org/10.1186/1472-6831-12-32

Untu, I., Chirita, R., Bulgaru-Iliescu, D., Chirila, B. D., Ciubara, A., & Burlea, S. L. (2015). Ethical Implications of Bio-Psycho-Social Transformations Entailed by the Aging Process. *Revista de Cercetare si Interventie Sociala, 48,* 216-225. https://www.rcis.ro/images/documente/rcis48_16.pdf

Velasco-Ortega, E., Monsalve-Guil, L., Casas-Barquero, N., Jimenez-Guerra, A., Torres-Lagares, D., & Segura-Egea, J. (2019). Salivary secretion in patients with schizophrenia. *Journal of biological regulators and homeostatic agents, 33*(3), 877-882. https://www.biolifesas.org/biolife/2019/06/24/salivary-secretion-in-patients-with-schizophrenia/

Yang, M., Chen, P., He, M. X., Lu, M., Wang, H. M., Soares, J. C., & Zhang, X. Y. (2018). Poor oral health in patients with schizophrenia: A systematic review and meta-analysis. *Schizophrenia research, 201*, 3-9. https://doi.org/10.1016/j.schres.2018.04.031

Wolff, A., Joshi, R. K., Ekström, J., Aframian, D., Pedersen, A. M. L., Proctor, G., Narayana, N., Villa, A., Sia, Y. W., Aliko, A., McGowan, R., Kerr, R. A., Jensen, S. B., Vissink, A., & Dawes, C. (2017). A guide to medications inducing salivary gland dysfunction, xerostomia, and subjective sialorrhea: a systematic review sponsored by the world workshop on oral medicine VI. *Drugs in R&D*, *17*(1), 1-28. https://doi.org/10.1007/s40268-016-0153-9