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Review Article

An Update Review to Cast Light on the Possible Role of Altered Oropharyngeal Microbiota in Differentiating True Psychosis from Malingered Psychosis in a Forensic Psychiatric Setting

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Over the past few years, malingered psychosis has had a progressive occurrence since a great deal of attention has been directed to the closures of long-stay psychiatric institutions and care in the community. Therefore, malingered psychosis needs to be identified to conduct precise forensic assessments and prevent miscarriages of justice and misuse of restricted healthcare resources. Although, over the past decades, researchers have introduced a number of workable psychometric strategies and tools for diagnosing true psychosis, it is still sometimes challenging to differentiate between true and malingered psychosis. Hence, identifying reliable and innovative diagnostic alternatives seems crucial. Accordingly, a summary of gathered evidence is provided by the present review for enhancing future evaluation of oropharyngeal microbiome composition as a practical indicator for diagnosing true psychosis in a forensic psychiatric setting. As per the systematic search terms (namely, "diagnostic marker," "oropharyngeal microbiome," "forensic psychiatric setting," "psychosis," and "oropharyngeal microbiota"), relevant English publications were searched from January 1, 1980, to September 15, 2023, in Scopus, the Web of Science, Embase, Cochrane Library, PubMed, and Google Scholar databases. Finally, eight articles were included in the present review. Also, we adopted the narrative technique so that the material synthesis leads to a cohesive and compelling story. The results revealed that the periodontal disease and saliva microbiome were possibly associated with true psychosis. Thus, since oropharyngeal microbial compositions are highly different among healthy controls and patients with true psychosis, future research can take advantage of saliva to differentiate between fake and true fake psychosis throughout the initial stages of forensic psychiatric assessment. As a substrate of interest, saliva could also be used for characterizing the various stages of psychosis under a forensic psychiatric setting.

1. Introduction

Malingered psychosis comprises the intentional falsification of psychiatric symptoms in order for the presenting patient to externally benefit in a tangible manner [1]. Since a wide range of clinical presentations constitutes the term "psychosis" [2], malingering patients mostly have a tendency for psychosis falsification instead of another form of disorder for gaining external benefits and induce clinicians to have a diagnostic dilemma, who often classify malingering with similar clinical phenomena and factitious disorders by delivering the benefit of the doubt [2, 3].

Individuals are regularly malingering psychosis to accomplish one of the subsequent goals: (i) criminals tend to avoid punishment through insanity pretension once they commit the crime, not competent enough to bear trial, deserving to be alleviated at sentencing, or innocent not to be executed; (ii) malingerers might keep attempting to exempt from the military service and its unwelcome assignments and inhibit combat; (iii) the odds are that malingerers fake psychosis to receive financial advantages from social security disability, gain workers' recompense, obtain compensation for damages of supposed psychological injury, or achieve veterans' benefits; (iv) prisoners are likely to malinger for receiving medication or being transferred to a psychiatric hospital to do "easier time" or evade facilitation; (v) it is probable that malingerers are moved to a psychiatric hospital for preventing arrest or receiving a courtesy room and board (identified as "three hots and a cot") [3].

Although the exact estimation of the quantity of malingered psychosis cases has been complicated [4], Cornell and Hawk [5] have illustrated that it might be prevalent among 8% of criminal defendants. Nonetheless, the malingered psychosis occurrence has increased over the past few years owing to the propensity for the closure of long-stay psychiatric institutions and care in the community [4]. Therefore, it is crucially required that forensic psychiatrists be able to identify malingered psychosis [6].

In this regard, major differences have been detected by recent scientific evidence in the oropharyngeal microbiota composition between healthy subjects and psychotic patients [7]. The hypothesis suggesting the feasible diagnostic role of oropharyngeal microbiota among patients with forensic and true psychosis seems almost likely based on the accessible evidence; however, no study has been carried out directly on how it works. Accordingly, a summary of gathered evidence is provided by the present review to enhance the future evaluation of oropharyngeal microbiome composition as a practicable indicator for diagnosing true psychosis in a forensic psychiatric setting.

2. Methods

The search strategy comprised an ancestry search [8] of oropharyngeal microbiome research on patients with psychosis and a systematic search in Scopus, the Web of Science, Embase, Cochrane Library, PubMed, and Google Scholar—we used these databases since they were relevant to oropharyngeal microbiota alterations in patients with psychosis, and additional results were not obtained by an exploratory search of other databases. Here, the search terms contained combinations of "forensic psychiatric setting," "diagnostic marker," "psychosis," "oropharyngeal microbiome," and "oropharyngeal microbiota." The eligibility of studies was confirmed based on (i) a type of assessment of oropharyngeal microbiome composition to be included among patients with true psychosis, (ii) a description of the oropharyngeal microbiome composition of patients with true psychosis in comparison with healthy controls, (iii) being published between January 1, 1980, and September 15, 2023, and (iv) having English language. Exclusion criteria were as follows: (i) review articles; (ii) hypothetical studies; (iii) case reports; (iv) not peer reviewed; (v) animal studies. A total of 34 articles were identified in the initial search after the removal of duplicate documents. Also, the excluded articles contained 20 reviews, 3 hypothetical articles, one case report, one animal study, and one preprint (a total of 26 articles) (see Figure 1). The appraisement of each of the selected articles was conducted precisely based on 10 assessment questions presented by Young and Solomon [9] (see Table 1). To reach a total score for each article, the authors then considered a specific score for each question, i.e., 1 for the assessment to be met and zero for not meeting the assessment or being unclear, as presented by poor (scores 3 or less), fair (scores 4 or 5), good (scores 6 to 8), and high quality (scores 9 or 10) (see Table 2). Lastly, we adopted the narrative technique so that the material yields a cohesive and compelling story. This depends on how MacLure [10] describes the engagement of a researcher with the material, i.e., reading, writing, thinking, interpreting, arguing, and justifying. These data were used to discuss crucial topics in this area, i.e., (i) the challenges faced to identify malingered psychosis, (ii) the connection between true psychosis and oropharyngeal microbiome composition, and (iii) the oropharyngeal microbiome composition's feasible diagnostic role among forensic psychiatric patients with true psychosis.

3. Results

3.1. Malingered Psychosis Identification and Its Challenges. The malingered psychosis diagnosis was a leading concern once forensic psychiatry was developing in the nineteenth century. A considerable number of clinical smoothing methods were introduced in this respect; nonetheless, during the twentieth century, the topic attractiveness faded away, apparently because of the wrong supposition about malingerers who fake symptoms in order to prevent imminent psychosis [4]. The subject has been largely ignored in the United Kingdom. Nevertheless, as the development of instruments was initiated in the 1980s (the first instrument was created during the previous century) with the ability to systematize clinical observations, forensic psychiatrists redirected significant attention towards malingering in the United States [4].

Over a forensic psychiatric assessment, malingered psychosis critically needs to be identified to prevent miscarriages of justice and misusing limited healthcare resources. It might be challenging to detect malingered psychosis,

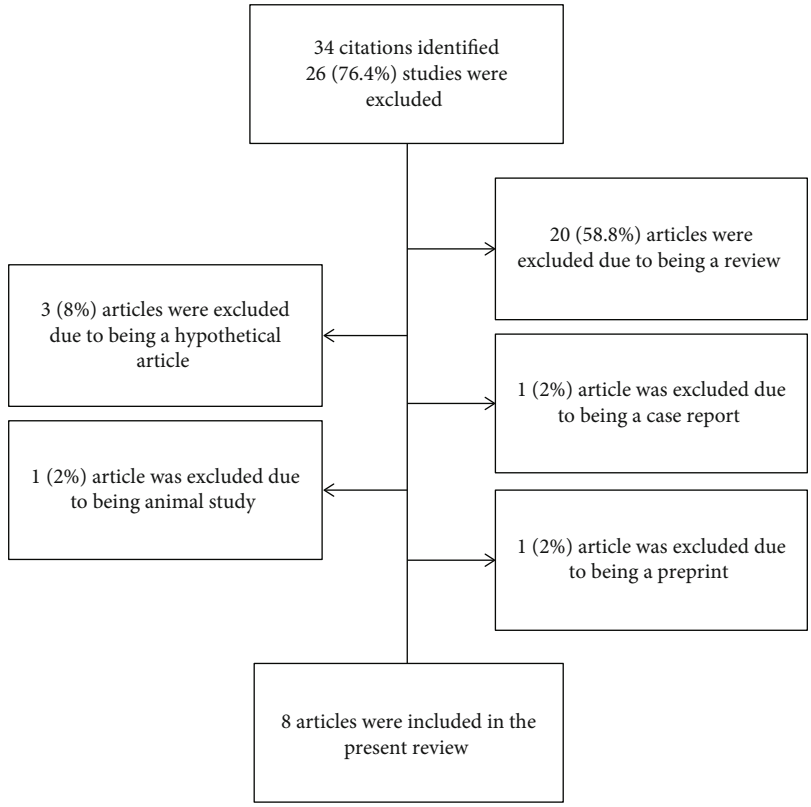

Figure 1: Articles selected to be included in the present review.

Table 1: Questions outlined by Young and Solomon to evaluate a research article [9].

(1) Is the study question relevant?
(2) Does the study add anything new?
(3) What type of research question is being asked?
(4) Was the study design appropriate for the research question?
(5) Did the study methods address the most important potential sources of bias?
(6) Was the study performed according to the original protocol?
(7) Does the study test a stated hypothesis?
(8) Were the statistical analyses performed correctly?
(9) Do the data justify the conclusions?
(10) Are there any conflicts of interest?

which entails a systematic approach. In order to confirm the existence of malingering psychotic symptoms in an individual, the clinician is required to review data from multiple sources and have a profound understanding of authentic psychotic symptoms. It is necessary that the clinician gather evidence from a comprehensive evaluation, clinical records, collateral data, and psychological testing. Although tremendous efforts are vital, the clinician is significantly responsible for assisting society in telling apart between true and malingering psychosis [1, 3]. Misdiagnosing a malingerer as authentically ill implies that they succeeded in obtaining unfair recompense or avoiding being responsible for criminal offenses. On the other hand, the mistaken classification of malingering may lead to injustice and cause psychiatric care to refuse the true psychosis of an individual needing treatment [3].

Three factors that hamper malingering detection were introduced by Millis and Putnam [11], including the risk of an expert's confirmatory bias or attribution error causing either over- or underdetection, a false clinical viewpoint on the capability of an individual to ascertain the probability of malingering at the time of a clinical rapport development, and simply using psychometric performance data. As shown by Hickling et al. [12], even clinicians with extensive experience encountered many challenges when detecting actors with illness simulation. Some evidence has also shown that clinicians are probably reluctant to label an individual a malingerer for a variety of explanations, e.g., fears of medico-legal consequences and worries about therapeutic relationships, possibly biasing clinicians into taking a more safer and conservative position [13]. Despite the development of some practical strategies and psychometric tools to resolve these restrictions, it is sometimes tough to distinguish patient claims [14, 15]. However, further reliable and innovative diagnostic alternatives are needed for the current limitations of the question-and-answer method to be transcended. In this regard, the present review highlights the oropharyngeal microbiome composition's feasible diagnostic role in differentiating true psychosis from malingered psychosis.

3.2. The Association between True Psychosis and Oropharyngeal Microbiome Composition. Human oral microbiota has

Table 2: A summary of the observed oropharyngeal microbiota differences between healthy controls and patients with psychosis.

Authors/year	Country	Study design	Objectives	Positive findings	Quality scores
Fawzi et al., 2011 [24]	Egypt	Case-control study 35 schizophrenic patients 35 healthy controls	Estimation of the prevalence and quantity of *Porphyromonas gingivalis* in the saliva of schizophrenic patients compared to healthy controls	A substantially higher *Porphyromonas gingivalis* prevalence was observed in schizophrenic patients' saliva compared to healthy subjects. As presented by PANSS scores, the levels of *Porphyromonas gingivalis* levels were largely associated with the severity of the schizophrenia psychopathology, where the most robust correlation was denoted by negative symptoms.	6
Shetty and Bose, 2014 [17]	India	Pilot observational exploratory study 250 schizophrenic patients (females = 110; males = 140)	Exploring the feasible bidirectional connection between periodontal disease and schizophrenia	The study indicated that patients with long histories of schizophrenia have exhibited periodontal conditions of poor quality, being demonstrated by plaque and gingival indexes. The obtained results implied the periodontal disease's feasible role in schizophrenia pathogenesis.	6
Yolken et al., 2015 [16]	United States	Case-control study 33 healthy controls 41 schizophrenic patients	Characterization of bacteriophage genomes in the oropharynx of healthy subjects and schizophrenic patients	*Lactobacillus phage phiadh* was significantly higher in schizophrenic patients compared to the controls. Among schizophrenic patients, the level of *Lactobacillus phage phiadh* level had a correlation with an escalated rate of comorbid immunological disorders.	7
Castro-Nallar et al., 2015 [19]	United States	Case-control study 16 healthy controls 16 schizophrenic patients	Characterization of schizophrenia microbiome through the interrogation of the oropharyngeal microbiome structure concerning its functional and taxonomic diversity	*Lactobacillus gasseri* was detected to have a higher prevalence in psychotic patients by a factor of 400 compared to controls; however, there were noticeably lower levels of *Neisseria*, *Haemophilus*, and *Capnocytophaga*.	7
Yolken et al., 2021 [21]	United States	Case-control study 121 schizophrenic patients 62 patients with mania 48 patients with major depressive disorder 85 healthy controls	Confirming the link between altered oropharyngeal microbiome and schizophrenia	The study revealed that the oropharyngeal microflora of schizophrenic and manic subjects was different from that of controls. *Neisseria subflava*, *Prevotella*, and *Weeksellaceae* were lessened in schizophrenic or manic patients compared with the controls; nonetheless, *Streptococci* were elevated in the former groups. Only manic patients showed that the unique pattern has appeared in *Schlegelella*. There was also a positive relationship between *Neisseria subflava* and cognitive functioning. There was an altered beta diversity in schizophrenic and manic patients, in comparison to healthy controls.	8

Table 2: Continued.

Authors/year	Country	Study design	Objectives	Positive findings	Quality scores
Qing et al., 2021 [22]	China	Case-control study 80 healthy controls 43 patients with clinical high risk 85 patients with first-episode schizophrenia	Exploring the salivary microbiome among schizophrenia patients Categorizing the microbial profiles at various schizophrenia's clinical stages Reaching an insight into the salivary microbes' role in the schizophrenia initiation	A high rate *Firmicutes*/*Proteobacteria* ratio was observed in the salivary microbiome among schizophrenic patients. A distribution of metabolic functions of the salivary microbiome was detected in schizophrenia. It is possible to assume differential metabolites as potential diagnostic biomarkers and show the severity of various clinical stages of the disease.	9
Cui et al., 2021 [32]	China	Case-control study 83 first-episode schizophrenic patients 42 clinically high-risk individuals for psychosis before its onset 78 healthy controls	Examining the link between salivary metabolomics and the schizophrenia onset	The results also revealed the earlier occurrence of oral metabolism disorder than the schizophrenia onset, which is intensified and concentrated with the disease initiation. The dysbiotic salivary microbiota may cause oral metabolism, leading to schizophrenia initiation through the redox system and the peripheral inflammatory response, highlighting the significance of the oral-brain connection in schizophrenia pathogenesis.	9
Lee et al., 2023 [23]	United States	Case-control study 9 patients with any psychotic bipolar disorder and schizophrenia-related psychosis 6 patients with nonpsychotic affective disorder 8 healthy controls	Investigating the association of oral and gut microbiome with clinical and molecular markers of schizophrenia	In this study, psychiatric cases had enrichment of pathogenic taxa and significantly higher heterogeneity of gut alpha diversity, similar to *Prevotella* and *Veillonella*, in the oral microbiome—a true categorizer of phenotype.	9

gained high interest due to the capability of inflammatory molecules, bacterial products, and oral bacteria for the human body invasion through the digestive tract or bloodstream [7]. In the present review, significant oropharyngeal microbiota discrepancies were observed between controls and psychotic patients (see Table 2). Compared to controls, a lactobacillus rise was shown in psychotic patients' samples [16]. *Lactobacillus gasseri* is the main host bacteria for *Lactobacillus phage phiadh*—identified as a common component of the oral and gastrointestinal mucosae—being able to bind to the intestinal epithelium. Various health advantages can be received by *Lactobacillus gasseri* through its antimicrobial activity, bacteriocin production, and the innate and adaptive systems' immunomodulation [17], which makes it possible for this bacterium to be positively employed as a probiotic [18]. *Lactobacillus gasseri* was found by Yolken et al. [16] to have a moderate correlation of various levels of *Lactobacillus phage phiadh*, implying a phage infection's lysogenic state in numerous cases. The virus reactivation can be provoked by diverse environmental conditions, which leads to the death of the host bacteria. Also, *Lactobacillus phage* is likely to possess other impacts on the bacteria ecology through controlling extra species of *Lactobacilli*. Despite the capability of some phages for immune system modulation regardless of their bacteria level modulation capability, *Lactobacillus phage phiadh* is ambiguous to have these properties. *Lactobacillus gasseri*, as this phage's host, was observed in higher prevalence in psychotic patients by a factor of 400 compared to controls [19, 20]; however, the levels of *Prevotella*, *Neisseria subflava*, and *Weeksellaceae* were noticeably lower [21]. By contrast, the levels of *Streptococcal* were more significant in psychotic cases [21]. A high *Firmicutes*/*Proteobacteria* ratio was also detected by Qing et al. [22] in the salivary microbiome among schizophrenic patients. In a new study, Lee et al. [23] showed that psychiatric cases had enrichment of pathogenic taxa and significantly higher heterogeneity of gut alpha diversity, similar to *Prevotella* and *Veillonella*, in the oral microbiome—a true

categorizer of phenotype. Compared to healthy controls, *Porphyromonas gingivalis* was also observed to be highly abundant in the saliva of schizophrenia patients [24], which leads to a neuroinflammation state [25, 26]. However, at this stage of knowledge, commenting on the existence of a bidirectional association between the oropharyngeal microbiome and the brain seems difficult [7]. All in all, more research is certainly required to cast light on a flawless answer to the rest of the questions in this scope.

3.3. The Oropharyngeal Microbiome Composition's Feasible Diagnostic Role among Forensic Psychiatric Patients with True Psychosis. Although no direct examination has been conducted on the oropharyngeal microbiome composition's feasible diagnostic role among forensic psychiatric patients with psychosis, it seems almost likely according to the accessible evidence [7, 16–26]. Our hypothesis can be explained by a neuroinflammation state present in psychotic patients [7]. In depth, immune and glial cells (i.e., neuroinflammation) can be activated by augmented inflammatory cytokine levels in the central nervous system by the periodontal disease through inducing the inflammatory process [25]. True psychosis pathogenesis may also be influenced by neuroinflammation [27]. The pathways such as molecular mimicry, antineuronal autoantibodies, proinflammatory cytokines, microglial activation, self-reactive T cells, and disturbance of the blood–brain barrier could be involved in true psychosis development [27–30]. A mechanistic association can exist between this innate inflammation and traditional monoaminergic, amplified oxidative injury, and glutamatergic abnormalities reported in true psychosis [27–30]. These findings suggested the role of the bacterial load and the periodontal disease-related inflammatory process in forming a state of neuroinflammation that aids the true psychosis onset [31]. Due to the restricted knowledge about the oropharyngeal microbiome composition's feasible diagnostic role in true psychosis [27], further research needs to be taken into account in a forensic psychiatric setting.

4. Discussion

The present review was carried out aiming to collect evidence to provide the opportunity to enhance the future evaluation of oropharyngeal microbiota composition as a practicable marker for the diagnosis of true psychosis in a forensic psychiatric setting. In this respect, a total of 8 articles including one pilot observational exploratory study and 7 case-control studies were investigated, which caused different themes to emerge. They have been grouped into four separate paragraphs, namely, the oropharyngeal phageome, periodontal disease, the salivary microbiome, and the oropharyngeal microbiome potentially linked with schizophrenia.

4.1. The Oropharyngeal Phageome. Among the microorganisms forming the microbiome, bacteriophages are viruses infecting bacteria and their replication and metabolism. Two types of phages exist in this regard: (i) virulent phages creating a lytic cycle causing its host death; (ii) temperate phages forming a lysogenic cycle, which involves their genome integration into the host chromosome for prophage development. The lysogenic phage's host bacterium is not ruined, but transmitting this genetic material. Nevertheless, the lysogenic cycle is able to shift to a lytic lifecycle under specific stress conditions [7]. Yolken et al. [16] metagenomically characterized bacteriophages from the oropharynx of schizophrenic patients, identifying merely one phage considerably larger in samples from schizophrenic patients irrespective of race, sex, age, smoking state, and socioeconomic status, i.e., *Lactobacillus phage phiadh* infecting *Lactobacillus gasseri*. A minimum of 1 *Lactobacillus phage phiadh* match was observed in 17 of 41 schizophrenic patients, whereas it was detected in 1 of 33 controls. Nonetheless, the link between *Lactobacillus phage phiadh* and schizophrenia still needs to be further examined, but Lactobacillus phage phiadh may modulate its host bacterium level, i.e., *Lactobacillus gasseri*, affecting the immune system of the host [7].

4.2. The Oropharyngeal Microbiome. Regarding the hypothesis that there might be an association or contribution between the oropharyngeal microbiome and an altered immune status in schizophrenia, a case-control study was conducted by Castro-Nallar et al. [19] for characterizing the schizophrenia oropharyngeal microbiome structure in terms of its functional and taxonomic diversity. At the phylum level, there is a higher share of *Firmicutes* in all samples from schizophrenic patients in comparison to controls who have a larger relative proportion of *Actinobacteria* and *Bacteroidetes*. Schizophrenic patients and the control group are almost similar in the case of relative proportions owned by other phyla such as *Proteobacteria* and *Fusobacteria*. In this study, smoking had no apparent impact on the microbiota composition at the phylum level. In terms of species quantity, the control group was richer, as compared to the schizophrenic sample; however, fewer species dominated it, contrary to schizophrenic patients [19]. Oropharyngeal samples were identified by a rise in lactic acid bacteria in schizophrenia (including *Bifidobacterium* and *Lactobacillus*), *Eubacterium*, and *Candida* accompanied by a substantial decrease in *Haemophilus*, *Capnocytophaga*, and *Neisseria* [19]. The former authors also detected an augmentation in the amount of *Lactobacillus gasseri*, seeming to be more prevalent in schizophrenic patients by a factor of 400 compared to controls. Castro-Nallar et al. [19] illustrated that the schizophrenic patients' microbiome was identified by an escalated quantity of metabolic pathways associated with metabolite transport systems such as glutamate, vitamin B12, and siderophores. On the contrary, lipid pathways, energy metabolism, and carbohydrate abounded in controls. It was revealed by Yolken et al. [21] that 121 schizophrenic patients had different pharyngeal microflora in terms of abundance and composition compared to controls, similar to those with other psychiatric disorders. Controls without a psychiatric diagnosis had considerably higher levels of *Weeksellaceae*, *Neisseria subflava*, and *Prevotella* compared to schizophrenic and manic patients. On the other hand, schizophrenic and manic patients showed higher levels of *Streptococci*, as well as an altered beta diversity, compared

to healthy controls. However, this study did not directly measure several environmental exposures that were probably raised in persons with psychiatric disorders [21]. Also, Lee et al. [23] found psychiatric cases with higher levels of pathogenic taxa, like *Prevotella* and *Veillonella*, substantially higher heterogeneity of gut alpha diversity in the oral microbiome, as a correct categorizer of phenotype. Cui et al. [32] also showed that the oral metabolism disorder takes place before the schizophrenia initiation and is intensified and concentrated with the brink of disease. They found that oral metabolism is likely to stem from the dysbiotic salivary microbiota and initiate schizophrenia through the redox system and peripheral inflammatory response, implying the significance of oral-brain linking in schizophrenia pathogenesis [32].

4.3. The Salivary Microbiome. The saliva acts as a paramount factor impacting the oral microbiome [7]. Lately, another case-control study [22] was conducted to examine the salivary microbiome concerning schizophrenia. In detail, they provided new data to cast light on the connection between schizophrenia initiation and salivary microbiome alterations. Three stages were identified by the authors, i.e., 85 first-episode schizophrenic patients, 43 clinically high-risk patients, and 80 healthy controls. This research aimed at characterizing the microbial profiles among these different groups. The presence of a large *Firmicutes*/*Proteobacteria* ratio was confirmed in the salivary microbiome among schizophrenic patients. The salivary of the first-episode schizophrenic group has a low beta diversity heterogeneity and high alpha diversity. In this case, the two other groups (clinically high-risk group and healthy controls) were analogous. Moreover, the authors stated that H2S-producing bacteria (or sulfate-diminishing bacteria) could act as a potential biomarker to detect first-episode schizophrenic and clinically high-risk patients since the elevated risk of schizophrenia initiation is correlated with the enrichment of H2S-producing bacteria in saliva. The H2S-producing bacteria enrichment could happen before the beginning of the disorder, which could be attributed to the schizophrenia's clinical manifestations (first-episode schizophrenia or weakened psychotic symptoms) as well. Eventually, the study demonstrated the distribution of the salivary microbiome's metabolic functions in schizophrenia; particularly, xenobiotic biodegradation pathways were severely diminished in the first-episode schizophrenic group.

4.4. Periodontal Disease. Since periodontal disease induced the inflammatory process, we incorporated a periodontal disease method to explore the connection between schizophrenia and oral microbiota. The common pathways of these disorders comprise proinflammatory cytokines, microglial activation, molecular mimicry, self-reactive T cells, disturbance of the blood–brain barrier, and antineuronal autoantibodies [7]. Innate inflammation is likely to have a mechanistical connection with the glutamatergic abnormalities and traditional monoaminergic and escalated oxidative injury observed in psychiatric illnesses [7]. In this regard, in their case-control study, Fawzi et al. [24] showed a substantially higher prevalence and quantity of *Porphyromonas gingivalis* in the saliva of schizophrenic patients in comparison to nonpsychiatric controls. Furthermore, a positive correlation was observed between severity of schizophrenia psychopathology and number of *Porphyromonas gingivalis* cells. Shetty and Bose [17] conducted a pilot observational exploratory study to investigate the feasible bidirectional connection between periodontal disease and schizophrenia. They assessed the periodontal status among 250 schizophrenic patients by investigating the following three parameters: Probe Pocket Depth, Plaque Index, and Gingival Index. All antipsychotically treated patients excluded a history of periodontal treatment or systemic disease. The analysis of the results was performed based on the schizophrenia duration; the maximum mean values of Gingival Index, Plaque Index, and Probe Pocket Depth were observed among the schizophrenic patients with an illness history of 11 years and more (being followed by 1–3 years of schizophrenia history, 4–6 years of schizophrenia history, and 7–10 years of schizophrenia history), where the differences in mean values between these groups were significant. Finally, the authors showed that schizophrenic patients were more prone to periodontal disease development, which can be increased by the drugs [17].

4.5. The Clinical Implications in the Psychiatric and Medical Practice. The clinical implications of the present review can be separated into two chief parts. Firstly, we believe that the changes in oropharyngeal microbiota composition that have been recognized as psychosis potential biomarkers might favor diagnosis. An insight into actual or predicted functional variations in metabolic pathways or microbial genes impact downstream clinical outcomes, and symptomatic expression is likely to contribute to differentiating between malingered psychosis and true psychosis in a forensic psychiatric setting and developing microbiome-targeted diagnostics for psychosis. Besides, the already available scarce data could be helpful in formulating new hypotheses and stimulating further research to better understand how immune-mediated abnormalities and microbiome contribute to the development of refractory psychosis and the introduction of novel treatment strategies [33–35].

4.6. Limitations and Challenges for Future Research. Some restrictions in recent studies and some challenges for future research were identified in the present review. Not even an included study suggested a formal causal association between the oropharyngeal microbiota and true psychosis attributable to myriad confusing biases, such as STDs (sexually transmitted diseases) with possible adverse effects on the mouth, specific environmental exposures impacting the microbiota, anticholinergic treatments, drug use (e.g., tobacco and cannabis), respiratory viruses, consuming alcohol, antioxidant-rich drugs (e.g., valproate, risperidone, clozapine, olanzapine, or lithium), diet (e.g., foods containing probiotics), and poor oral hygiene prevalent in psychotic patients [17, 36–42]. As an example, Fawzi et al. [24] showed a correlation between lower education levels and *Porphyromonas gingivalis*. Also,

there is a momentous correlation between *Porphyromonas gingivalis* detection and smoking [24]. Castro-Nallar et al. [19] conducted their research only on nonsmoker controls, which can lead to mistaking the impacts of smoking for psychosis effects. Although the lower prevalence levels of *Capnocytophaga* and *Neisseria* were linked to smoking [43, 44], it is not easy to confirm a connection with mental illness. Further studies need to be conducted in the future for controlling confounding factors, including diet, comorbidities, and treatment for defining primary microbiome changes (i.e., with an intrinsic implication in the pathophysiology of schizophrenia) or secondary microbiome changes (e.g., to life habits). Future research will face another challenge originating from the obtained results by Cui et al. [32]. They found the oral metabolism to occur before the schizophrenia onset and showed that it is intensified and concentrated with the disease initiation [32]. The dysbiotic salivary microbiota may cause the oral metabolism, leading to schizophrenia initiation through the redox system and the peripheral inflammatory response [32], suggesting a big challenge in clarifying the promising role of altered oropharyngeal microbiota in differentiating true psychosis from malingered psychosis in a forensic psychiatric setting. No studies have also examined whether microbiome dissimilarities could act as schizophrenia biomarkers. Moreover, analogously discordant patterns of alterations were identified by investigating the gut microbiome in depression, as well as a level of overlap with variations observed in schizophrenia [45, 46]. The potential diagnostic practicality of the data is limited by this lack of specificity.

5. Conclusions

The present paper is intended to review studies on the association between the pathophysiology of psychosis and oropharyngeal microbiome composition. As another objective, the oropharyngeal microbiome composition's feasible diagnostic role was explored in detecting true psychosis in a forensic psychiatric setting. The obtained results revealed that the periodontal disease and the saliva microbiome were potentially associated with true psychosis. Thus, since oropharyngeal microbial compositions are highly different between healthy controls and patients with true psychosis, future research can take advantage of saliva to differentiate between fake and true psychosis during the early stages of forensic psychiatric assessment. As a substrate of interest, saliva could also be used for characterizing the diverse psychosis stages in a forensic psychiatric setting.

Data Availability

The data are available from the corresponding author on a reasonable request.

Conflicts of Interest

No conflict of interest is declared by the authors.

Authors' Contributions

MKH, DDB, SS, SM, AA, NJ, ZG, MN, and NR have conceived and written the manuscript, revised it in the present version, and collected the references.

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