Periodontal disease and effects of antipsychotic medications in patients newly diagnosed with schizophrenia: a population-based retrospective cohort

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Abstract

Aim. Compared with the general population, individuals with schizophrenia have a higher risk of periodontal disease, which can potentially reduce their life expectancy. However, evidence for the early development of periodontal disease in schizophrenia is scant. The current study investigated risk factors for periodontal disease in patients newly diagnosed with schizophrenia.

Methods. We identified a population-based cohort of patients in Taiwan with newly diagnosed schizophrenia who developed periodontal disease within 1 year of their schizophrenia diagnosis. Treatment with antipsychotics and other medications was categorised according to medication type and duration, and the association between medication use and the treated periodontal disease was assessed through logistic regression.

Results. Among 3610 patients with newly diagnosed schizophrenia, 2373 (65.7%) had an incidence of treated periodontal disease during the 1-year follow-up. Female sex (adjusted odds ratios [OR] 1.40; 95% confidence interval [CI] 1.20–1.63); young age (adjusted OR 0.99; 95% CI 0.98–0.99); a 2-year history of periodontal disease (adjusted OR 2.45; 95% CI 1.84–3.26); high income level (adjusted OR 2.24; 95% CI 1.64–3.06) and exposure to first-generation (adjusted OR 1.89; 95% CI 1.54–2.32) and secondary-generation (adjusted OR 1.33; 95% CI 1.11–1.58) antipsychotics, anticholinergics (adjusted OR 1.24; 95% CI 1.03–1.50) and antihypertensives (adjusted OR 1.91; 95% CI 1.64–2.23) were independent risk factors for periodontal disease. Hyposalivation – an adverse effect of first-generation antipsychotics (FGAs) (adjusted OR 2.00; 95% CI 1.63–2.45), anticholinergics (adjusted OR 1.27; 95% CI 1.05–1.53) and antihypertensives (adjusted OR 1.90; 95% CI 1.63–2.22) – was associated with increased risk of periodontal disease. Therefore, hypersalivation due to FGA use (adjusted OR 0.72; 95% CI 0.59–0.88) was considered a protective factor.

Conclusions. The current study highlights that early prevention of periodontal disease in individuals with schizophrenia is crucial. Along with paying more attention to the development of periodontal disease, assessing oral health regularly, helping with oral hygiene, and lowering consumption of sugary drinks and tobacco, emphasis should also be given by physicians to reduce the prescription of antipsychotics to the extent possible under efficacious pharmacotherapy for schizophrenia.

Introduction

Mortality risks associated with physical illnesses, especially cardiometabolic health, in patients with schizophrenia are attracting increased attention (Mitchell et al., 2013; Carney et al., 2016). By contrast, the periodontal health of patients with schizophrenia has remained overlooked (Arnaiz et al., 2011; Wey et al., 2016). Compared with the general population, patients with schizophrenia have a high incidence of periodontal disease (Kenkre and Spadigam, 2000; Ramon et al., 2003; Hu et al., 2016). Although periodontal disease is not an acutely life-threatening disease, an increasing body of evidence supports its association with...
cardiovascular disease, stroke, metabolic syndrome, pulmonary disease and adverse pregnancy outcomes (Pihlstrom et al., 2005; Cullinan and Seymour, 2013).

Periodontal disease – including gingivitis and periodontitis – is inflammation of the periodontium due to a persistent bacterial infection that leads to the breakdown of connective tissue and bone – a major cause of tooth loss in adults (Pihlstrom et al., 2005; Thomson et al., 2012; Ji et al., 2015). In the general population, recognised risk factors for periodontal disease include aged, male sex, race, unhealthy lifestyle (poor oral hygiene, smoking and alcohol use), poor nutrition (inadequate dietary consumption of calcium and vitamin D), systemic diseases (obesity, metabolic syndrome, osteoporosis, diabetes mellitus and HIV/AIDS), psychosocial stress, genetic factors and medications (Albandar, 2002; Pihlstrom et al., 2005; Thomson et al., 2012; Genco and Borgenakke, 2013). Antipsychotics and other medications affect salivary secretion often causing hyposalivation or hypersalivation. Salivary secretion dysfunction aggravates periodontal disease (Sekine et al., 1999; Hashimoto et al., 2012; Eltas et al., 2013). Only a few studies have assessed the link between antipsychotics and periodontal disease in patients with schizophrenia to date (Gopalakrishnapillai et al., 2012; Eltas et al., 2013). Therefore, the current study investigated this link.

Most research on periodontal disease and schizophrenia has been restricted to cross-sectional designs and small-to-medium samples; they have also focused on chronic schizophrenia (Arnaiz et al., 2011; Gurbuz et al., 2011; Teng et al., 2011; Gopalakrishnapillai et al., 2012; Eltas et al., 2013; Shetty and Bose, 2014; Nayak et al., 2016; Wey et al., 2016). The literature cannot fully explain the progress of development of periodontal disease in individuals with schizophrenia, especially the early stages of development. Given the lack of extensive literature, we identified a population-based cohort of patients newly diagnosed with schizophrenia from the Taiwan National Health Insurance Research Database (NHIRD), determined how many developed periodontal disease within 1 year of their diagnosis, and identified risk factors associated with periodontal disease.

Methods

Study source and participants

Detailed descriptions of the Taiwan NHIRD sample and study procedures have previously been published (Hu et al., 2016; Lin et al., 2018). In summary, we employed the 1995–2010 NHIRD data, a subset composed of 1 million randomly sampled beneficiaries drawn in 2000. The Internal Review Board approved the study and informed consent was waived because we used de-identified medical information from the NHIRD.

We performed a cohort study of patients who were newly diagnosed with schizophrenia between 1 January 2000 and 31 December 2009. The patients were diagnosed based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code 295 by at least two psychiatrists and such patients had been treated with antipsychotics for more than 3 months. The index date was defined as the date of the schizophrenia diagnosis. Exclusion criteria were as follows: HIV/AIDS, diabetes mellitus, chronic pulmonary disease, osteoporosis and alcoholism before the index date (because of the potential confounding factors for periodontal disease) (Albandar, 2002; Pihlstrom et al., 2005; Hu et al., 2016). Additionally, a 2-year history of periodontal disease before the index date was recorded.

Incidence of treated periodontal disease after their index date

Claim records of periodontal disease of the participants comprised both the periodontal disease-related diagnoses (ICD-9-CM codes 523.0–523.5, 523.8 and 523.9) and anatomical therapeutic chemical codes diagnosed by dentists (91001C, 91003C, 91004C, 91006C–91008C, 91009B, 91010B, 91011C–91013C, 91104C, 92033C, P4001C and P4002C). The incidences of periodontal disease in participants diagnosed with and treated for periodontal disease within 1 year after their index date were recorded. We followed up all participants for 1 year until a diagnosis of periodontal disease, end of follow-up in medical records, death or the end of 2010.

Exposure to antipsychotics and other medications

Appendix Table A1 presents antipsychotics and other medications in this study. We acquired these medication data from prescription files and estimated the pharmacotherapy duration based on the dosing regimen of each patient and the number of units dispensed. All medications were classified into four categories: first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs), anticholinergics and antihypertensives. Exposure to antipsychotics and other medications was recorded if a participant was prescribed the same medication for at least 4 weeks during the 1-year follow-up. Co-medications were considered as concomitant drugs that were simultaneously prescribed with antipsychotics and other medications.

The risk of periodontal disease for each antipsychotic and other medication was evaluated to identify adverse effects (hyposalivation and hypersalivation) following usage. The adverse effects of continuous medication use on periodontal disease were assessed. The potential adverse effects of antipsychotics and other medications are listed in Appendix Table A2 (Friedlander and Marder, 2002; Scully and Bagan, 2004; Muenck and Hamer, 2012; Vinayak et al., 2013).

Statistical analysis

All statistical analyses were performed using SAS statistical software (v 9.1, SAS Institute, Cary, NC, USA). Patients with schizophrenia who did and did not develop periodontal disease were analysed using the Pearson’s $\chi^2$ test after stratification by sex, age, geographical region, income level, medical prescriptions and a 2-year history of periodontal disease. To analyse the independent effect of schizophrenia on the risk of developing periodontal disease, we used logistic regression after adjustment for sex, age, geographical region, income level, concomitant medical prescriptions, 2-year history of periodontal disease, potentially associated risk factors and index date. Moreover, we performed hierarchical logistic modelling using SAS GLMMIX to mitigate potential collinearity among sexes, geographical region and income level (Dai et al., 2006). We used logistic regressions for evaluating the individual odds ratios (ORs) of periodontal disease related to the adverse effects of antipsychotics and other medications and potentially associated risk factors. A two-sided statistical significance level of $p < 0.05$ was used in all analyses.

Results

During the study period, 3610 patients were newly diagnosed with schizophrenia. The mean age at presentation was 34.7 years
The incidence of periodontal disease in patients with schizophrenia varies with ethnicity, time, socioeconomic status, psychophysical condition, definition and length of illness and assessment tools (Angelillo et al., 1995; Tang et al., 2004; Pihlstrom et al., 2005; Arnaiz et al., 2011; Gurbuz et al., 2011; Teng et al., 2011). The following three studies – including the current study – among ethnic Chinese populations are considered as examples (Tang et al., 2004; Teng et al., 2011). A cross-sectional survey of oral health in central Taiwan using the community periodontal index (CPI) showed that 90% of psychiatric inpatients (schizophrenia: 61%, length of illness: approximately 6 years) had poor periodontal health (Teng et al., 2011). A dental study in Hong Kong demonstrated that 98.5% of inpatients with chronic schizophrenia (length of illness: 20 years) had poor periodontal health, as assessed using the standardised dental evaluation of the World Health Organization (Tang et al., 2004). In the current study, the incidence of periodontal disease in patients with newly diagnosed schizophrenia (length of illness: 1 year or less) in Taiwan was 65.7%, as assessed from dentist visit records. Although time, duration of schizophrenia, assessment tools, psychophysical condition and socioeconomic status were different in all three studies, the data crudely illustrated that in terms of duration of schizophrenia, the incidence of periodontal disease in patients with schizophrenia increases from 65.7% after approximately 1 year to 98.5% after 20 years from the schizophrenia diagnosis. The results possibly imply that early preventive measures could prevent the incidence of periodontal disease in approximately one-third of patients newly diagnosed with schizophrenia.

### Risk factors for periodontal disease in schizophrenia

Most evidence demonstrates that old age (Angelillo et al., 1995; Tang et al., 2004; Arnaiz et al., 2011; Gurbuz et al., 2011; Teng et al., 2011) and male sex (Gurbuz et al., 2011; Gopalakrishnanpillai et al., 2012) are associated with significantly higher risks of periodontal disease in patients with schizophrenia. This evidence was obtained from patients with chronic schizophrenia and periodontal disease by using assessment tools such as the CPI. Therefore, we assessed the presence of periodontal disease by identifying dentist visits by patients within 1 year of a schizophrenia diagnosis. Differences between subjects and assessment tools may have led to the identification of young age and female sex as risk factors for treated periodontal disease in our study. In other words, young female patients in the early stage of schizophrenia may have an opportunity or good insights for treatment of periodontal disease with good prognosis. On the contrary, elderly male patients with chronic schizophrenia had poor periodontal health. The findings thus suggest that primary care staff should be more concerned about early prevention of periodontal disease in elderly male patients with schizophrenia because this population may not visit a dentist frequently and their periodontal disease could worsen when they enter the chronic stage of schizophrenia.

Low income level is a known crucial risk factor for periodontal disease in the general population (Pihlstrom et al., 2005). However, high income level was a risk factor for treated periodontal disease in patients with newly diagnosed schizophrenia – probably because the patients belonged to a high income level class in this study were well aware that dental visits are necessary for maintaining good oral hygiene. The financial burden of dental expenses was limited for the patients in our study because Taiwan’s National Health Institutes provide most Taiwanese with basic dental care without large copayments (Teng et al., 2011). Notably, 2-year history of periodontal disease was the most vital risk factor for periodontal disease in the current study. Therefore, the incidence of periodontal disease increased dramatically from 9% at 2 years before schizophrenia diagnosis to 39.5% in the 1 year after. This increase might be ascribed to the effect that psychiatric treatment can provide to a patient – increasing in a patient’s sense of reality and willingness to seek...
treatment for periodontal disease, leading to more than 6-fold dental visits – albeit with the adverse effects of antipsychotics.

**Antipsychotics and periodontal disease in schizophrenia**

Little evidence is available about the adverse effects of antipsychotics and periodontal disease in patients with schizophrenia because most previous surveys had small-to-medium samples, and complex patterns of antipsychotics were prescribed to the study subjects (Hede, 1995; Gurbuz et al., 2011; Teng et al., 2011; Gopalakrishnapillai et al., 2012; Eltas et al., 2013). The current paper is among the few reports (Hede, 1995; Gopalakrishnapillai et al., 2012) that investigate the effects of antipsychotics on periodontal disease in patients with schizophrenia. It was impossible to assess the effect of each antipsychotic; we classified all antipsychotics and other medications into four categories: FGAs, SGAs, anticholinergics and antihypertensives. The findings of the current study illustrated that all four types of medication could accelerate development of periodontal disease, and the order of high to low risk is as follows: antihypertensives, FGAs, SGAs and anticholinergics. Extrapyramidal symptoms often occur with antipsychotics, particularly FGAs, so physicians prescribe co-medications such as anticholinergics or antihypertensives to alleviate these symptoms (Teng et al., 2011; Gopalakrishnapillai et al., 2012; Hu et al., 2016). Unfortunately, anticholinergics and antihypertensives can exacerbate the resultant periodontal disease. Therefore, clinicians should prescribe antipsychotics and other medications to the least extent possible under efficacious pharmacotherapy for schizophrenia.

**Strengths and limitations of the study**

The major strength of the current study was the use of a large population-based cohort that enabled us to evaluate the relationship between antipsychotics and risk factors for periodontal disease in the early stages of schizophrenia. The findings may prove favourable to prevent the development of periodontal disease in patients with schizophrenia, especially the ethnic Chinese population. The well-determined temporal relationship between antipsychotic prescription and the occurrence of periodontal disease was another strength of this study. We obtained not only rigorous illness diagnoses but also correct medication information from the NHIRD. The benefit of using periodontal disease as a surrogate is switched to requiring medical attention. Our findings demonstrated that hyposalivation induced by FGA, anticholinergic and antihypertensive is potentially associated with increased risk of periodontal disease; hence, FGA-induced hypersalivation in periodontal disease is considered a protective factor. Although our statistical analyses could not provide sufficient information on the linked pharmacopathology between the adverse effects of saliva and periodontal disease, the data demonstrate how clinicians can reduce periodontal disease caused by the adverse effects of antipsychotics during pharmacotherapy for schizophrenia. The findings suggest that clinicians should avoid iatrogenic adverse effects on saliva while prescribing antipsychotics as far as possible and actively manage the adverse effects and ensure early dental referral. The possible underlying causal pharmacological mechanism must be determined in future studies.
as HIV/AIDS, diabetes mellitus, osteoporosis, chronic pulmonary diseases and a history of periodontal disease.

This study had several limitations. First, diagnoses of both periodontal disease and schizophrenia could have been underestimated, for instance, because of Berkson's bias, in which hospital cases and controls in a case–control study can be systematically different from one another because the combination of exposure to risk and disease occurrence increases the likelihood of admission. Hence, we surveyed treated patients with schizophrenia as well as the possible consequences of periodontal disease. Accordingly, treatment-naïve patients may have had only a limited effect on our analysis. Second, patient adherence to medications could not be evaluated because of the prescription claims database in this study. However, medication nonadherence would most likely have resulted in a nondifferentiated misclassification of exposure leading to possible underestimation of actual risk. Third, only treated periodontal disease indicated by the patients’ medical records was considered as the measure of periodontal disease occurrence in this study as opposed to all cases of periodontal disease wherein patients with schizophrenia developed periodontal disease but did not visit a dentist. Fourth, nonavailability of information on dietary, lifestyle and other potential risk factors for periodontal disease, such as illness severity, biochemistry data and patients’ unhealthy lifestyles such as tobacco consumption and poor oral hygiene (Albandar, 2002; Ramon et al., 2003; Scully and Bagan, 2004; Pihlstrom et al., 2005; Dumitrescu et al., 2008; Chu et al., 2012; Kossioni et al., 2012; Thomson et al., 2012; Genco and Borgnakke, 2013; Morales-Chávez et al., 2014; Hu et al., 2016) – was considered.

## Table 3. Risk of periodontal disease in patients with newly diagnosed schizophrenia during 1-year follow-up

| Risk Factor                  | OR * | 95% CI       | P    |
|------------------------------|------|--------------|------|
| Age                          | 0.99 | 0.98–0.99    | <0.001|
| Sex (female v. male)         | 1.40 | 1.20–1.63    | <0.001|
| Monthly income               |      |              |      |
| Low income (v. no income)    | 0.98 | 0.82–1.16    | 0.783 |
| High income (v. no income)   | 2.24 | 1.64–3.06    | <0.001|
| Geographical region of Taiwan|      |              |      |
| Central (v. Northern)        | 1.03 | 0.84–1.25    | 0.802 |
| Southern (v. Northern)       | 0.71 | 0.60–0.84    | <0.001|
| Eastern and others (v. Northern) | 0.68 | 0.44–1.06   | 0.088 |
| A 2-year history of          |      |              |      |
| Periodontal disease (v. no)  | 2.45 | 1.84–3.26    | <0.001|
| Prescriptions                |      |              |      |
| FGAs (v. no)                 | 1.89 | 1.54–2.32    | <0.001|
| SGAs (v. no)                 | 1.33 | 1.11–1.58    | 0.001 |
| Anticholinergics (v. no)     | 1.24 | 1.03–1.50    | 0.025 |
| Antihypertensives (v. no)    | 1.91 | 1.64–2.23    | <0.001|

OR, odds ratio; CI, confidence interval.

*After adjustment for age, sex, income level, geographical region, 2-year history of periodontal disease, index date and concomitant prescriptions.

## Table 4. Adjusted ORs of periodontal disease in patients with newly diagnosed schizophrenia due to potential hyposalivation and hypersalivation caused by antipsychotics and other medications

| Prescriptions     | OR * | 95% CI       | P    |
|-------------------|------|--------------|------|
| FGAs              |      |              |      |
| Hyposalivation     | 2.00 | 1.63–2.46    | <0.001|
| Hypersalivation    | 0.72 | 0.59–0.88    | 0.001 |
| SGAs              |      |              |      |
| Hyposalivation     | 1.24 | 0.96–1.60    | 0.104 |
| Hypersalivation    | 1.10 | 0.87–1.38    | 0.423 |
| Anticholinergics  |      |              |      |
| Hyposalivation     | 1.27 | 1.05–1.53    | 0.015 |
| Antihypertensives  |      |              |      |
| Hyposalivation     | 1.90 | 1.68–2.22    | <0.001|

OR, odds ratio; CI, confidence interval.

*After adjustment for age, sex, income level, geographical region, 2-year history of periodontal disease, index date and concomitant prescriptions.

## Conclusions

In this paper, we highlight early prevention of periodontal disease in patients with schizophrenia. Based on our findings and previously reported evidence, we suggest that more care should be provided to men with schizophrenia who have a history of periodontal disease so as to prevent further periodontal degeneration. We also emphasise that in addition to paying more attention to development of periodontal disease, assessing oral health regularly, assisting with oral hygiene and lowering consumption of sugary drinks and tobacco, physicians should prescribe antipsychotics to the least extent possible and avoid iatrogenic adverse effects on saliva as far as possible under efficacious pharmacotherapy for schizophrenia.

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## Author contributions

J.-H. Tsai and K.-F. Hu designed the study and wrote the protocol. J.-H. Tsai, Y.-H. Chou, P.-S. Ho, C.-H.R. Lin and H.-Y. Chuang interviewed and assessed the database. J.-H. Tsai, K.-F. Hu and P.-S. Ho managed the literature, analysed and wrote the manuscript and tables. P.-S. Ho, C.-H.R. Lin and H.-Y. Chuang analysed the data statistically. All authors have contributed to and have approved the final manuscript.

## Financial support

None.

## Conflict of interest

None.

## Ethical standards

This study was approved by the Institutional Review Board at Kaohsiung Medical University Hospital (KMUH-IRB-EXEMPT-20140030) and informed consent was waived because of the use of previously stored de-identified medical information from the NHIRD.

## Availability of data and materials

In the current study, there are ethical or legal restrictions on sharing a de-identified data set. Therefore, we have provided contact information for a data access committee, see NHIRD_SQL Generator: http://sqlgen.net.nsysu.edu.tw/SQI_Generator/General_Searching.html (in English, cited on 2019/2/13).
References

Albandar JM (2002) Global risk factors and risk indicators for periodontal disease. Periodontology 2000 29: 177–206.

Angelillo IF, Nobile CG, Pavia M, De Fazio P, Puca M and Amati A (1995) Dental health and treatment needs in institutionalised psychiatric patients in Italy. Community Dentistry and Oral Epidemiology 23, 360–364.

Arnaiz A, Zumárraga M, Díez-Altuna I, Uriarte JJ, Moro J and Angelillo IF, Nobile CG, Pavia M, De Fazio P, Puca M and Amati A (2016) Cardiometabolic risk factors in young people at ultra-high risk for psychosis: a systematic review and meta-analysis. Schizophrenia Research 170, 290–300.

Carney R, Cotter J, Bradshaw T, Firth J and Yung AR (2012) Comparison of oral health between inpatients with schizophrenia and disabled people or the general population. Journal of the Formosan Medical Association 111, 214–219.

Cullinan MP and Seymour GJ (2013) Periodontal disease and systemic illness: will the evidence ever be enough? Periodontology 2000 62, 271–286.

Dai J, Li Z and Rocke D (2006) Hierarchical Logistic Regression Modeling with SAS GLIMMIX. Available at http://www.lexjansen.com/wuss/2006/Analytics/ANL-Dai.pdf (Accessed 18 November 2017).

Dumitrescu AL, Dogaru CB and Dogaru CD (2008) Instability of self-esteem and affective liability as determinants of self-reported oral health status and oral health-related behaviors. The Journal of Contemporary Dental Practice 9, 38–45.

Eltas A, Kartalci S, Eltas SD, Dündar S and Uslu MO (2013) An assessment of periodontal health in patients with schizophrenia and taking anti-psychotic medication. International Journal of Dental Hygiene 11, 78–83.

Friedlander AH and Marder SR (2002) The psychopathology, medical management and dental implications of schizophrenia. The Journal of the American Dental Association 133, 603–610.

Genco RJ and Borgnakke WS (2013) Risk factors for periodontal disease. Periodontology 2000 62, 59–94.

Gopalakrishnapillai AC, Iyer RR and Kalantharakath T (2011) Oral health and the symptoms of schizophrenia. Psychiatry Research 188, 24–28.

Hirotomi T, Yoshihara A, Ogawa H, Ito K, Igarashi A and Miyazaki H (2012) Prevalence of periodontal disease among inpatients in a psychiatric hospital in India. Hede B (1995) Oral health in Danish hospitalized psychiatric patients. Community Dentistry and Oral Epidemiology 23, 44–48.

Hirotomi T, Yoshihara A, Ogawa H, Ito K, Igarashi A and Miyazaki H (2006) A preliminary study on the relationship between stimulated saliva and periodontal conditions in community-dwelling elderly people. Journal of Dentistry 34, 692–698.

Hu KF, Chou YH, Wen YH, Hsieh KP, Tsai JH, Yang P, Yang YH and Lin CR (2016) Antipsychotic medications and dental caries in newly diagnosed schizophrenia: a nationwide cohort study. Psychiatry Research 245, 45–50.

Ji S, Choi YS and Choi Y (2015) Bacterial invasion and persistence: critical events in the pathogenesis of periodontitis? Journal of Periodontal Research 50, 570–585.

Kenkre AM and Spadigam AE (2000) Oral health and treatment needs in institutionalized psychiatric patients in India. Indian Journal of Dental Research 11, 5–11.

Kossion AE, Kossionis GE and Polychronopoulos A (2012) Oral health status of elderly hospitalised psychiatric patients. Gerodontology 29, 272–283.

Lin CR, Tsai JH, Wu SS, Chang YP, Wen YH, Liu JS and Lung FW (2018) Quantitative comorbidity risk assessment of dementia in Taiwan: a population-based cohort study. Medicine (Baltimore) 97, e0298.

Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W and De Hert M (2013) Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders – a systematic review and meta-analysis. Schizophrenia Bulletin 39, 306–318.

Morales-Chávez MC, Rueda-Delgado YM and Peña-Orozco DA (2014) Prevalence of bucco-dental pathologies in patients with schizophrenia disorder. Journal of Clinical and Experimental Dentistry 6, e7–e11.

Muench J and Hamer AM (2012) Adverse effects of antipsychotic medications. American Family Physician 81, 617–622.

Nayak SU, Singh R and Kota KP (2016) Periodontal health among non-hospitalized chronic psychiatric patients in Mangaluru City-India. Journal of Clinical and Diagostic Research 10, ZC40–ZC43.

Pihlstrom BL, Michalowicz BS and Johnson NW (2005) Periodontal diseases. Lancet 366, 1809–1820.

Ramon T, Grinshpoon A, Zusman SP and Weizman A (2003) Oral health and treatment needs of institutionalized chronic psychiatric patients in Israel. European Psychiatry 18, 101–105.

Scully C and Bagan JV (2004) Adverse drug reactions in the orofacial region. Critical Reviews in Oral Biology and Medicine 15, 221–239.

Sekine Y, Rikihisa T, Ogata H, Echizen H and Arakawa Y (1999) Correlations between in vitro affinity of antipsychotics to various central neurotransmitter receptors and clinical incidence of their adverse drug reactions. European Journal of Clinical Pharmacology 55, 583–587.

Shetty S and Bose A (2014) Schizophrenia and periodontal disease: an oculo-neural connection? A cross-sectional epidemiological study. Journal of Indian Society of Periodontology 18, 69–73.

Tagk KG, Sun FC, Unqvari GS and O’Donnell D (2004) Oral health of psychiatric in-patients in Hong Kong. International Journal of Social Psychiatry 50, 186–191.

Teng PR, Su JM, Chang WH and Lai TJ (2011) Oral health of psychiatric inpatients: a survey of central Taiwan hospitals. General Hospital Psychiatry 33, 253–259.

Thomson WM, Sheiham A and Spencer AJ (2012) Sociobehavioural aspects of periodontal disease. Periodontology 2000 60, 54–63.

Vinayak V, Annigeri RG, Patel HA and Mittal S (2013) Adverse effects of drugs on saliva and salivary glands. Journal of Orofacial Sciences 5, 15–20.

Wagaiyu EG and Ashley FP (1991) Mouthbreathing, lip seal and upper lip coverage and their relationship with gingival inflammation in 11–14 year-old schoolchildren. Journal of Clinical Periodontology 18, 698–702.

Wey MC, Loh S, Doss JG, Abak Bakar AK and Kisdely S (2016) The oral health of people with chronic schizophrenia: a neglected public health burden. Australian and New Zealand Journal of Psychiatry 50, 685–694.
### Table A1. ICD-9-CM codes and Anatomical Therapeutic Chemical [ATC] classification system codes used in this study

| Main diseases                      | ICD-9-CM codes and ATC codes |
|------------------------------------|-------------------------------|
| Schizophrenia                      | 295                           |
| Periodontal disease                | 523.0–523.5, 523.8, 523.9, 91001C, 91003C, 91004C, 91006C–91008C, 91009B, 91010B, 91011C–91013C, 91104C, 92033C, P4001C, P4002C |
| Exclusion comorbidity              | ICD-9-CM codes                |
| Osteoporosis                       | 733.0                         |
| Diabetes mellitus                  | 250                           |
| AIDS                               | 042, 079.53, 795.71           |
| Alcoholism                         | 291, 303.0X, 303.9, 305.00–305.03, 357.5, 425.5, 535.30, 535.31, 571.0–571.5, 571.8, 571.9, 790.3, 980.0, 980.2, 980.8, 980.9, 977.3, V11.3 |
| Chronic pulmonary disease          | 416.8, 416.9, 490, 491–495, 496, 500–505, 506.4, 508.1 |
| Drug categories                    | ATC codes                     |
| FGAs                               |                               |
| Chlorpromazine (HCl)               | N05AA01                       |
| Trifluoperazine (HCl) or (2HCl)    | N05AB06                       |
| Thioridazine HCl                   | N05AC02                       |
| Haloperidol                        | N05AD01                       |
| Flupentixol (2HCl)                 | N05AF01                       |
| Chlorprothixene HCl                | N05AF03                       |
| Thiothixene                         | N05AF04                       |
| Pimozide                           | N05AG02                       |
| Loxapine (succinate)               | N05AH01                       |
| Sulpiride                          | N05AL01                       |
| SGAs                               |                               |
| Ziprasidone                        | N05AE04                       |
| Risperidone                        | N05AX08                       |
| Clozapine                          | N05AH02                       |
| Olanzapine (micronized)            | N05AH03                       |
| Quetiapine (fumarate)              | N05AH04                       |
| Amisulpride                        | N05AL05                       |
| Zotepine                           | N05AX11                       |
| Aripiprazole                       | N05AX12                       |
| Paliperidone                       | N05AX13                       |
| Anticholinergics                   |                               |
| Trihexyphenidyl HCl                | N04AA01                       |
| Biperiden HCl                      | N04AA02                       |
| Diphenhydramine                    | R06AA52                       |
| Diphenhydramine HCl                | R06AA52                       |
| Antihypertensives                  |                               |
| Furosemide                         | C03CA01                       |
| Propranolol HCl                    | C07AA05                       |
| Carteolol HCl                      | C07AA15                       |
| Atenolol                           | C07AB03                       |
| Enalapril maleate                  | C09AA02                       |
| Drug categories        | Hyposalivation | Hypersalivation |
|-----------------------|----------------|-----------------|
| FGAs                  |                |                 |
| Chlorpromazine (HCl)  | +              | 0               |
| Trifluoperazine (HCl) or (2HCl) | +  | 0 |
| Thioridazine HCl      | +              | +               |
| Haloperidol           | +              | +               |
| Flupentixol (2HCl)    | +              | 0               |
| Chlorprothixene HCl   | +              | 0               |
| Thiothixene           | +              | 0               |
| Pimozide              | +              | 0               |
| Loxapine (succinate)  | +              | 0               |
| Sulpiride             | +              | 0               |
| SGAs                  |                |                 |
| Ziprasidone           | +              | 0               |
| Risperidone           | +              | +               |
| Clozapine             | +              | +               |
| Olanzapine (micronized)| +  | + |
| Quetiapine (fumarate) | +              | +               |
| Amisulpride           | +              | 0               |
| Zotepine              | +              | 0               |
| Aripiprazole          | +              | 0               |
| Paliperidone          | +              | +               |
| Anticholinergics      |                |                 |
| Trihexyphenidyl HCl   | +              | 0               |
| Biperiden HCl         | +              | 0               |
| Diphenhydramine       | +              | 0               |
| Diphenhydramine HCl   | +              | 0               |
| Antihypertensives     |                |                 |
| Furosemide            | +              | 0               |
| Propranolol HCl       | +              | 0               |
| Carteolol HCl         | +              | 0               |
| Atenolol              | +              | 0               |
| Enalapril maleate     | +              | 0               |

+ = yes, 0 = no.