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First-generation antipsychotics use and reduced risk of pneumonia—Clinical implications in SARS-CoV2 treatment: A systematic review and meta-analysis of observational studies

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ABSTRACT

The use of antipsychotics (AP) has been linked to nearly 60% increase in the incidence of pneumonia. The study purposes to devise safest treatment regimens for psychiatric patients with underlying respiratory comorbidities. A systematic literature search was conducted. A total of 41 studies were evaluated, which included 33 articles for meta-analysis. The quality of retrieved articles was screened by reviewing independently. The risk of bias in each study was assessed using the Newcastle–Ottawa Scale. Inter-rater agreement calculation was performed using Rayyan QCRI. Statistical analysis was performed using R 4.0.3. The meta-analysis conducted revealed that the risk of pneumonia (OR = 1.66; 95% CI = 1.64–1.68) and respiratory failure (OR = 1.79; 95% CI = 1.61–2.00) were higher in psychotropic users compared to nonusers. Pneumonia risk was higher in second-generation antipsychotic users (OR = 1.12; 95% CI = 1.01–1.25) compared to other antipsychotic users. However, no association was found between first-generation antipsychotics and pneumonia compared to other psychotropic exposure (OR = 0.93; 95% CI = 0.86–0.99). Chlorpromazine, sulpiride, and aripiprazole were found to be statistically safer compared to other AP. AP should be of appropriate choice in patients with SARS-CoV-2 infection, recurrent pneumonia history or those with opportunistic infections.

INTRODUCTION

In India, the prevalence rate for psychiatric disorders ranges from 9.5 to 370 per 1,000 individuals, and these differences in prevalence rates have also been documented in international studies (Polanczyk *et al*., 2015). Psychotropic medications are commonly prescribed to the elderly population; moreover, the major reported cause of death in this particular population was community-acquired pneumonia (CAP), whereas the use of antipsychotics (AP) has been associated with an increased incidence of pneumonia (Christodoulou and Kalaitzi, 2005). When comparing second-generation antipsychotics (SGA) to first-generation antipsychotics (FGA), SGA was associated with an increased incidence of pneumonia (Gau *et al*., 2010; Knol *et al*., 2008). Benzodiazepines (BZD) have also been associated with an increased incidence of CAP and death from it (Obiora *et al*., 2013). An elevated risk of respiratory-related morbidity and mortality was significant in case of selective serotonin reuptake inhibitors (SSRI) or selective norepinephrine reuptake inhibitors (SNRI) drugs (Vozoris *et al*., 2018).

The COVID-19 pandemic and the associated uncertainty could potentially increase the likelihood of mental illnesses and exacerbate health inequalities (Moreno *et al*., 2020). According to a recent study, a psychiatric epidemic is coexisting with the COVID-19 pandemic, necessitating the attention of the international health community (Hossain *et al*., 2020). Therefore, it is a crucial need to identify AP with minimal risk of causing respiratory infections and respiratory depression.

The meta-analysis by Dzahini *et al*. (2018) showed that exposure to AP, both FGA and SGA, was associated with an

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increased risk for pneumonia. However, the study did not take into consideration the use of any other psychotropic drug classes. However, this has been taken into account in our study. Our study assessed the association between the use of psychotropic agents and their effect on the respiratory function in patients with psychiatric disturbances and figured out the antipsychotic drug associated with minimal risk of pneumonia and respiratory depression. The rational and practical principles described here can also favor optimal management of psychotropic agents for COVID-19 patients, maintaining control of the underlying psychiatric condition, preventing the chances of aggravation of respiratory symptoms in these patients, mitigating the potentially aggravating effects of psychotherapy, reducing the length of hospital stay, and helping improve the patient's quality of life.

MATERIALS AND METHODS

We followed the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) checklist to report the systematic review and meta-analysis of observational studies. The study protocol was registered with the International Prospective Register of Systematic Reviews number CRD42021234283.

Study eligibility and selection criteria

We included all case control studies, nested case control studies, retrospective and prospective cohort studies, case-crossover studies, and observational studies fulfilling the inclusion criterion. Studies available in English, observational studies reporting psychotropic drug usage, studies reporting original quantitative data associated with the relative incidence or mortality from respiratory failure, pneumonia or any other respiratory illness in patients prescribed with at least one psychotropic compared to those not prescribed any psychotropics were statistically analyzed (e.g., 95% confidence intervals, CIs). Studies reporting the use of psychotropic drugs in patients with bipolar disorder I and II, schizophrenia, major depressive disorder, cyclothymia, generalized anxiety disorder, panic attack, social anxiety, posttraumatic stress, substance abuse, and any other psychiatric disturbances were included. Participants included elderly, adults, and children with a psychotropic prescription. We did not restrict the participation to pregnancy and children. However, we excluded case reports, case series, reviews, and articles that did not report any kind of respiratory illness incidence and studies not available in English and articles with only abstract.

Intervention/Exposure

Psychotropic drugs included antipsychotic agents, mood stabilizers, benzodiazepines, SSRIs, tricyclic antidepressants and opioids.

Search strategy and selection of primary studies

We searched electronic databases, including PubMed, Scopus, Cochrane Central Register of Controlled Trials, Embase, LILACS, Google Scholar, MEDLINE, Science Direct, Web of Science, and DOAJ, for observational studies meeting the inclusion criterion. The search strategy combined terms of various respiratory illnesses, such as pneumonia, and various classes of psychotropic medication names. The searches were restricted to articles available only in English.

Retrieval of the articles was followed by quality screening by two independent reviewers. Studies with an inter-rater reliability of more than 90% were included in the analysis. Full-text articles of the included studies were obtained and screened. We discussed eligibility until consensus was achieved and was also reviewed by a third independent author, who acted as an arbiter. Statistical measures of association (odds ratio), relative risk, and attributable risk were extracted from the retrieved articles. Baseline demographics and clinical characteristics of patients were also extracted, if available, for subgroup analysis. The reference section of the relevant primary studies, systematic reviews, and guidelines were searched to identify any additional studies.

Study quality and data extraction

The potential risk of bias in each study was assessed by using the Newcastle–Ottawa Scale (NOS). It assessed the quality of methods used in the identification of groups, comparability (confounding bias), and ascertainment of the exposure in case control studies or outcome in cohort studies. Inter-rater agreement calculation was performed by using Rayyan QCRI. The data were extracted based on events in exposed group, events in unexposed group, total number of samples in exposed group, and total number of samples in the unexposed group.

Statistical analysis

Heterogeneity was assessed by visual inspection of the forest plots and I^2 statistics. An I^2 value of 50% was considered significant. We primarily used odds ratio as the measure of association between psychotropic drugs usage and onset of respiratory insufficiency in patients. Publication bias was determined by using Egger's test and funnel plot. Forest plots of both fixed-effects and random-effects models were used to determine the effect of psychotropic medications on respiratory function. Exploring the confounding factors contributing to heterogeneity, such as age group, comorbidities, gender, smoking status, and concomitant medications, to determine the effect of the variables on the onset of respiratory insufficiency in patients was planned; however, due to the limited number of studies under each comparison, such tests were undependable due to lower power and hence were not conducted. However, subgroup analysis was performed to identify AP with minimal risk of respiratory deficits. All statistical analyses were performed using R 4.0.3 version.

RESULTS

A total of 968,673 records were identified through the electronic database search using the keywords psychotropic, AP, respiratory failure, and pneumonia. After applying the exclusion criteria, 41 studies were included in the systematic review (see Fig. 1 and Table 1). Of the 41 studies included, 8 were excluded based on the NOS for risk of bias assessment. Thus, finally, 33 studies were included in the meta-analysis. Of these, 11 studies (n = 196,008) assessed the association between antipsychotic drug usage and risk of pneumonia; 11 studies (n = 1,797,641) assessed the association between benzodiazepines, non-benzodiazepines, and pneumonia; 2 studies (n = 88,580) assessed the association between antidepressant drug use and pneumonia risk; 4 studies (n = 25,392) assessed the association between prescribed opioid

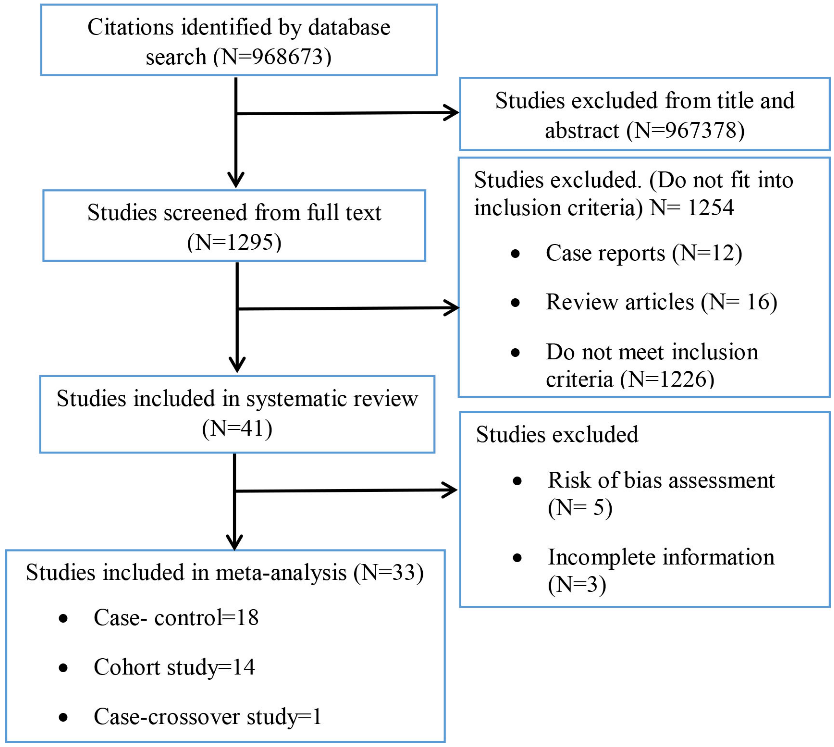

Figure 1. PRISMA flowchart for inclusion of articles in the systematic review and meta-analysis.

exposure and pneumonia, recurrent pneumonia due to antipsychotic exposure; 2 studies (n = 12,039) assessed the association between antipsychotic drug exposure and respiratory failure; and 2 studies (n = 24,737) assessed the association between benzodiazepine exposure and respiratory failure. Different methods were adopted by each study to identify the patient population which included medical records, health insurance database, general practice patient databases, and nursing home records.

Assessment of quality of studies

The quality of the nonrandomized study included in the systematic review/meta-analysis was evaluated using the NOS as recommended by the Cochrane Handbook. This scale assessed the quality of methods used in the selection of study groups, comparability of the groups, ascertainment of exposure in case control studies, and outcome in cohort studies. Each study was rated and awarded using a star scoring system, with a maximum of nine stars for good quality studies. The studies were independently reviewed by three reviewers and any discrepancy was resolved by discussions. The articles were reviewed using the web application Rayyan QCRI, a tool designed to collaborate and create systematic reviews (Ouzzani *et al*., 2016). The review was conducted for each objective: psychotropic agents induced pneumonia (34 articles) and psychotropic agents induced respiratory failure (7 articles). Based on the inclusion and exclusion criteria and Newcastle–Ottawa assessment, the list of studies to be included in the systematic review was finalized. Five articles were excluded based on the decisions of independent reviewers.

Assessment of publication bias

Funnel plots are visual tools for investigating publication bias. It shows a scattered plot of the different studies in meta-analysis with odds ratio given on the horizontal x-axis and standard error on the vertical y-axis. Funnel plots were used to assess the publication bias in psychotropic drug exposure versus no exposure (Fig. 2); SGA exposure versus other psychotropic drug exposure (Fig. 3); FGA exposure versus other psychotropic drug exposure (Fig. 4); and risk of respiratory failure associated with psychotropic drug exposure versus no exposure (Fig. 5).

Heterogeneity assessment

Heterogeneity of the studies was assessed by the visual representation of forest plots, and the fraction of variance was estimated using I^2 statistics. Eleven articles contained data to compare the psychotropic drug exposed population (n = 350,728) with the nonexposed population (n = 2,460,405) to evaluate the risk of pneumonia following psychotropic drug exposure (Fig. 6). The risk of pneumonia was increased by psychotropic drug exposure (OR = 1.66; 95% CI 1.64–1.68; 11 studies). Five articles contained data to assess the risk of pneumonia associated with FGA exposure (n = 19,211) compared to other psychotropic drug exposure (n = 15,894) (Fig. 7). FGAs have a lower risk of pneumonia compared to other psychotropic drug exposures (OR = 0.93; 95% CI = 0.86–0.99; 5 studies). Six articles contained data to assess the risk of pneumonia associated with SGA exposure (n = 11,139) compared to other psychotropic drug exposures (n = 14,402) (Fig. 8). SGAs had an increased risk of pneumonia compared to other psychotropic drug exposures (OR = 1.12; 95% CI = 1.01–1.25; 6 studies). Risk of respiratory failure associated with psychotropic exposure was assessed by comparing the psychotropic drug exposed group (n = 9,618) to the nonexposed group (n = 16,219) with two articles (Fig. 9). Risk of respiratory failure was increased with exposure to psychotropic drugs (OR = 1.79; 95% CI = 1.61–2.00; 2 studies).

Table 1. Summary of the studies included in the systematic review and meta-analysis.

Study (year)	Study design	Sample size (subjects enrolled)	Age group	Psychotropic included	Respiratory illness identified	Inclusion in Meta-analysis
Hennessy *et al*. (2007)	Case control	Cases, 12,044 Control, 48,176	≥65	Antidepressant, AP, Barbiturate, BZD, Mood stabilizer, Opiate	Pneumonia	Yes
Yang *et al*. (2013)	Case control	Cases, 571 Control, 2,277	15–65	FGA, SGA, Mood Stabilizers	Pneumonia	Yes
Knol *et al*. (2008)	Case control	Cases, 543 Control, 2,163	≥65	FGA, SGA	Pneumonia	Yes
Gau *et al*. (2010)	Case control	Cases, 194 Control, 952	≥65	SGA	CAP	Yes
Trifiro *et al*. (2010)	Case control	Cases, 258 Control, 1,686	≥ 65	FGA, SGA	CAP	Yes
Hung *et al* (2016)	Case control	Cases, 487 Control, 1,438	18–65	FGA, SGA, BZD, Antidepressant, Mood Stabilizers	Recurrent Pneumonia	Yes
Obiora *et al*. (2013)	Case control	Cases, 4,964 Control, 29,697	<25, >75 25–75	BZD, Zopiclone	Pneumonia	Yes
Almirall *et al*. (1999)	Case control	Cases, 205 Control, 475	>14	BZD	CAP	Yes
Almirall *et al*. (2008)	Case control	Cases, 1,336 Control, 1,326	>14	BZD	CAP	Yes
Dublin *et al*. (2011)	Case control	Cases, 1,039 Control, 2,022	65–94	Opioids, BZD	Pneumonia	Yes
Wang *et al*. (2017b)	Case control	Cases, 4,533 Control, 16,388	≥20	BZRA, Z Drugs	Pneumonia	Yes
Chen *et al*. (2017)	Case control	Cases, 4,533 Control, 16,388	≥20	BZD, BZD Anxiolytics, Non-BZD Hypnotics, Zopiclone	Pneumonia	Yes
Cheng *et al*. (2018)	Case control	Cases, 2,501 Control, 9,961	18–65	AP, Mood stabilizers, Antidepressant, BZD	Pneumonia	Yes
Jung *et al*. (2016)	Case control	Cases, 51,029 Control, 188,391	≥65	BZD, Non-BZD	Pneumonia	Yes
Edelman *et al*. (2019)	Case control	Cases, 4,246 Control, 21,146	Mean age,55	Opioids	CAP	Yes
Vozoris *et al*. (2018)	Cohort Study	Cases, 28,360 Control, 28,360	≥66	SSRI, SNRI	Pneumonia	Yes
Huybrechts *et al*. (2011)	Cohort Study	*N* = 10,900	≥65	FGA, SGA, Antidepressant, BZD	Pneumonia	No
Rohde *et al*. (2019)	Cohort Study	FGA, 8,355 SGA, 8,001	Mean 26.3–40.6	FGA, SGA	Pneumonia	Yes
Kim *et al*. (2017)	Cohort Study	FGA, 1,126 SGA, 2,580	≤4, ≥75 4–74	FGA, SGA	Pneumonia	Yes
Barnett *et al*. (2006)	Cohort Study	*N* = 14,057	≥65	FGA, SGA, Antidepressant, Mood Stabilizers	Pneumonia	No
Jackson *et al*. (2015)	Cohort Study	FGA, 9,060 SGA, 17,137	≥65	FGA, SGA	Pneumonia	Yes
Setoguchi *et al*. (2008)	Cohort Study	FGA, 12,882 SGA, 24,359	≥65	FGA, SGA	Pneumonia	Yes
Rafaniello *et al*. (2014)	Cohort Study	SGA, 1,618	≥65	SGA	Pneumonia	No
Star *et al*. (2010)	Cohort Study	Unclear	≥65, ≥80 18–64	FGA, SGA	Pneumonia	No
Brunnstrom *et al*. (2009)	Cohort Study	Unclear	Median 80	Unclear	Pneumonia	No
Huybrechts *et al*. (2012b)	Cohort Study	FGA, 7,463 SGA, 76,496	≥65	FGA, SGA	Pneumonia	No

Countinued

Study (year)	Study design	Sample size (subjects enrolled)	Age group	Psychotropic included	Respiratory illness identified	Inclusion in Meta-analysis
Aparasu *et al*. (2013)	Cohort Study	FGA, 3,609 SGA, 3,609	≥65	FGA, SGA	Pneumonia	Yes
Mehta *et al*. (2015)	Cohort Study	SGA, 92,234	≥65	SGA	Pneumonia	Yes
Pratt *et al*. (2011)	Cohort Study	FGA, 807 SGA, 1,107	≥65	FGA, SGA	Pneumonia	Yes
Kuo *et al*. (2012)	Cohort Study	Case, 1,739 Control, 6949	18-65	FGA, SGA	Pneumonia	Yes
Tolppanen *et al*. (2016)	Cohort Study	*N* = 60,584	34–105	AP	Pneumonia	No
Nakafero *et al*. (2016)	Cohort Study	*N* = 804,337	<18, >65 18–65	BZD, Zopiclone	Pneumonia	Yes
Maeda *et al*. (2016)	Cohort Study	Triazolam, 1,3015 Non-triazolam, 411,610	65–74 ≥75	Triazolam	Pneumonia	Yes
Taipale *et al*. (2017)	Cohort study	BZD, 5,232 Z drugs, 3,269	≥85, <65 65–84	BZD, Z drugs	Pneumonia	Yes
Wang *et al*. (2020)	Case control	Cases, 7,084 Control, 12,785	≥20	Antidepressant, Barbiturates, BZD	ARF	Yes
Chen *et al*. (2015)	Case control	Cases, 2,434 Control, 2,434	≥65	BZRA	Respiratory Failure	Yes
Wang *et al*. (2017a)	Case cross-over study	Cases, 5,032 Control, 5,032	≥40	AP, Opioids	ARF	Yes
Ciranni *et al*. (2009)	Cohort Study	SGA, 1,569 FGA, 407	18–65	FGA, SGA	Respiratory depression	Yes
Huybrechts *et al*. (2012a)	Cohort Study	*N* = 75,445	≥65	FGA, SGA	Unclear	No
Chen *et al*. (2011)	Cohort Study	*N* = 3,796	18–64	Unclear	Pneumonia ARF	Yes
Kales *et al*. (2007)	Cohort Study	*N* = 10,615	>65	FGA, SGA, Other Psychotropics	Pneumonia	Yes

AP: Antipsychotics; FGA: First-generation antipsychotics; SGA: Second-generation antipsychotics; CAP: Community-acquired pneumonia; ARF: Acute respiratory failure; BZD: Benzodiazepines; BZRA: Benzodiazepine receptor agonists.

Subgroup analysis

The risk of pneumonia for 10 individual drugs having ≥2 articles was calculated. All the SGAs, including risperidone (OR = 1.08; 95% CI = 1.00–1.17), olanzapine (OR = 1.30; 95% CI = 1.19–1.42), clozapine (OR = 1.85; 95% CI = 1.44–2.36), quetiapine (OR = 1.26; 95% CI = 1.15–1.38), zotepine (OR = 1.24; 95% CI = 0.92–1.66), and amisulpride (OR = 1.20; 95% CI = 1.01–1.42), have an increased risk of pneumonia following its usage compared to other psychotropics. However, aripiprazole had a lower risk (OR = 0.63; 95% CI = 0.48–0.81) (Fig. 12), but the results were statistically insignificant, with $p = 0.4$. FGAs, such as haloperidol (OR = 1.65; 95% CI = 1.14–2.38), have an increased risk of pneumonia; however, chlorpromazine (OR = 0.81; 95% CI = 0.60–1.10) (Fig. 10) and sulpiride (OR = 0.84; 95% CI = 0.70–1.01) (Fig. 11) had a lower risk of pneumonia compared to other psychotropic drug usage.

DISCUSSION

Respiratory disorders caused by psychotropic medications are of significant concern in the current era of the pandemic driven by SARS-CoV-2 infection (Bilbul *et al*., 2020). While few case control studies have linked antipsychotic therapy to severe breathing difficulties, acute respiratory distress, or acute respiratory failure, long-term use of SGA has been associated with an increased risk of pneumonia (Bilbul *et al*., 2020; Wang *et al*., 2017a). Our meta-analysis of observational studies determined significant association between psychotropic drug usage and onset of pneumonia (OR = 1.66; 95% CI = 1.62–1.70; $p = 0.04$). The results of our meta-analyses are on par with a previous meta-analysis that reported an 83% increased risk in pneumonia with antipsychotic usage (Haddad and Correll, 2018). However, in the subgroup analysis, we observed associations contrary to that reported. A 12% higher risk of pneumonia was noted with the use of SGAs, while the risk of pneumonia was found to be reduced by 7% with the use of FGAs. These results are contrary to those reported previously in the literature, which associated a relatively higher risk of pneumonia with SGAs to FGAs. Our study is the first meta-analysis to report a reduced risk of pneumonia with the use of FGAs.

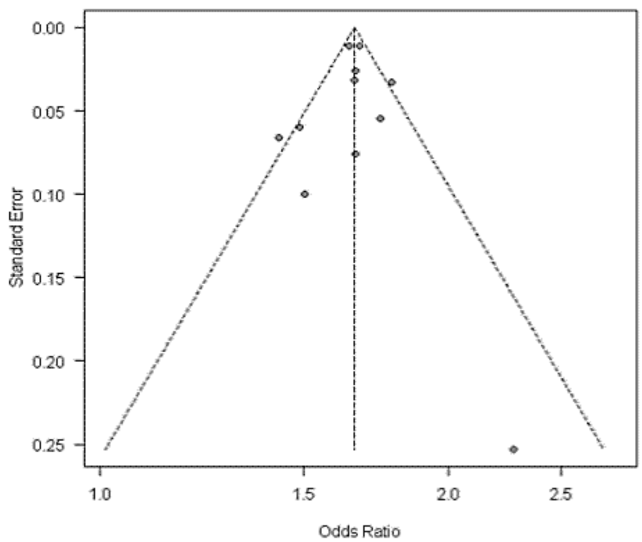

Figure 2. Funnel plot of risk of pneumonia in psychotropic use versus no use.

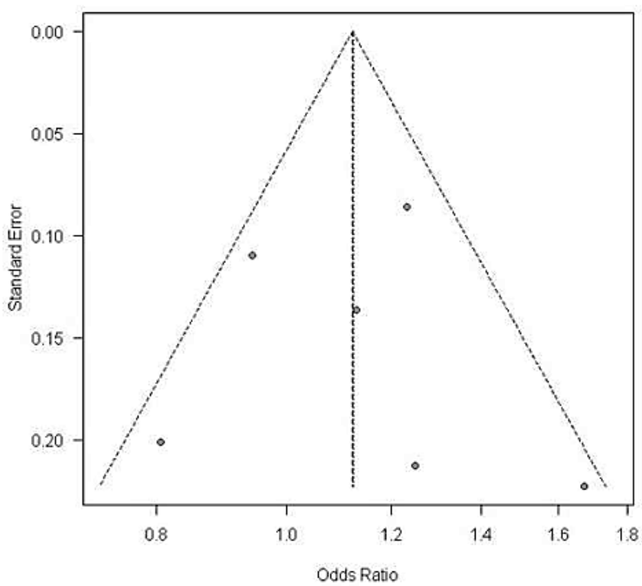

Figure 3. Funnel plot of risk of pneumonia with SGAs versus other psychotropic drug use.

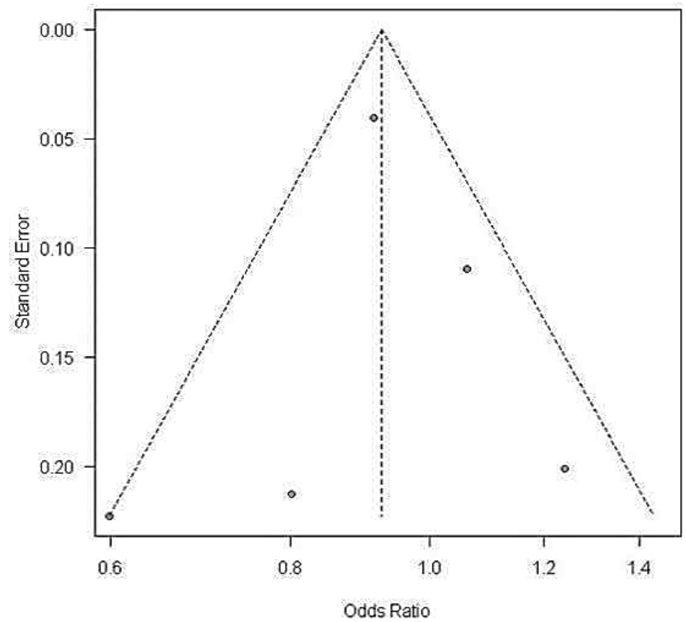

Figure 4. Funnel plot of risk of pneumonia with FGAs versus other psychotropic drug use.

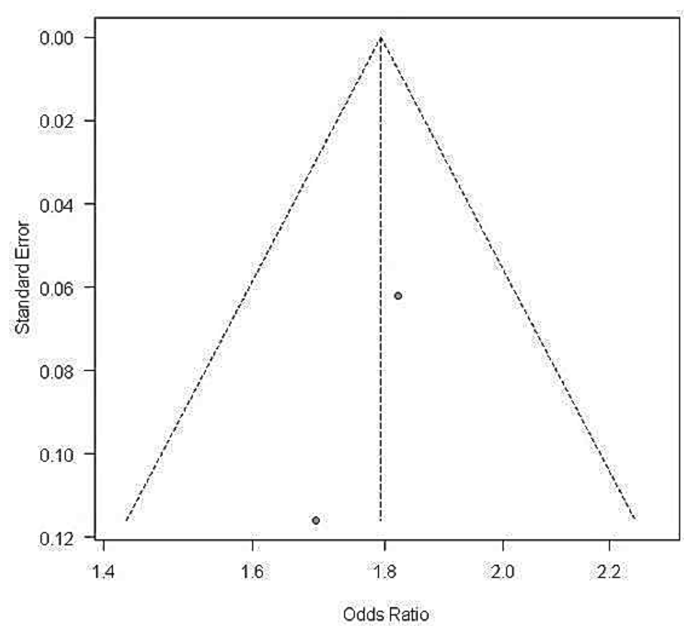

Figure 5. Funnel plot of risk of respiratory failure with psychotropic drug use versus no use.

Potential pharmacological mechanisms

Extrapyramidal side effects may be a possible predisposing factor for pneumonia, especially aspiration pneumonia (Marik and Kaplan, 2003). The dopamine receptor blocking activity of FGAs is linked to the extrapyramidal symptoms (EPS) (Farah, 2005). The main EPS related to increased pneumonia risk was tardive dyskinesia (Rajamaki *et al*., 2020). Affinities of AP for neurotransmitter receptors, particularly the muscarinic-1 (M1) and histaminergic-1 (H1) receptors, may be associated with AP use and pneumonia (Hals *et al*., 1988). SGAs, such as clozapine, owing to their affinity for H1 receptor or anticholinergic action, are associated with increased pneumonia risk (Kuo *et al*., 2013). Xerostomia causing impaired oropharyngeal bolus transport was another possible mechanism (Cicala *et al*., 2019). Also, the effect of AP on cytokine production, difference in the antibody production causing immunosuppressive action, and association with immunological effects of the drug raised the risk of infections, including pneumonia (May *et al*., 2019; Pollmächer *et al*., 2000). Blockage of the D2 receptors can induce dystonia in the larynx, which in turn can precipitate difficulty in breathing and stridor in the patients (Lewis and O'Day, 2021). Previous case series evaluation has found an association between neuroleptic malignant syndrome and AP use (Wilson and Ridley, 2007). The risk for pneumonia was increased in the presence of several peripheral BZD receptors (Wang *et al*., 2017b). A possible mechanism to explain the risk involves normal pharyngeal function impairment,

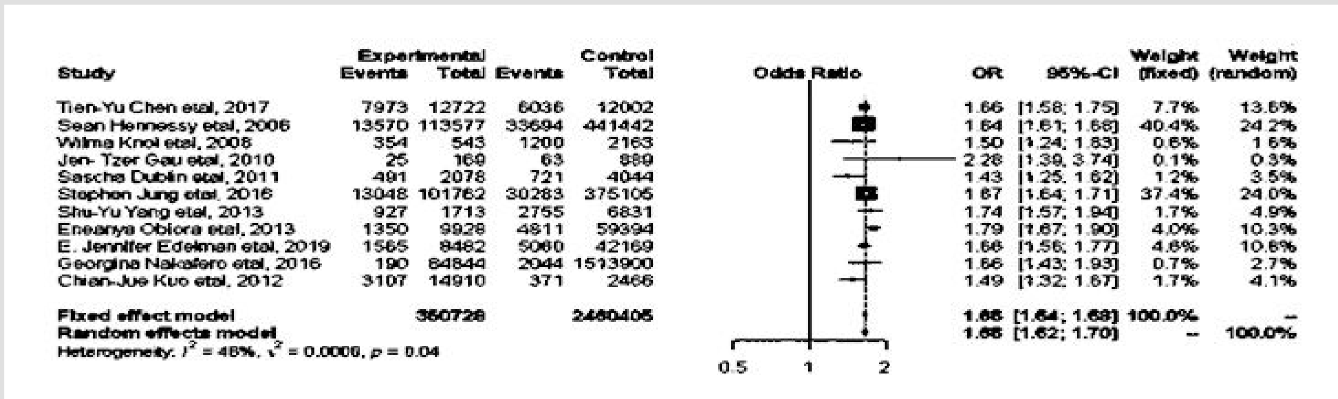

Figure 6. Risk of pneumonia with psychotropic drug exposure versus no psychotropic drug exposure.

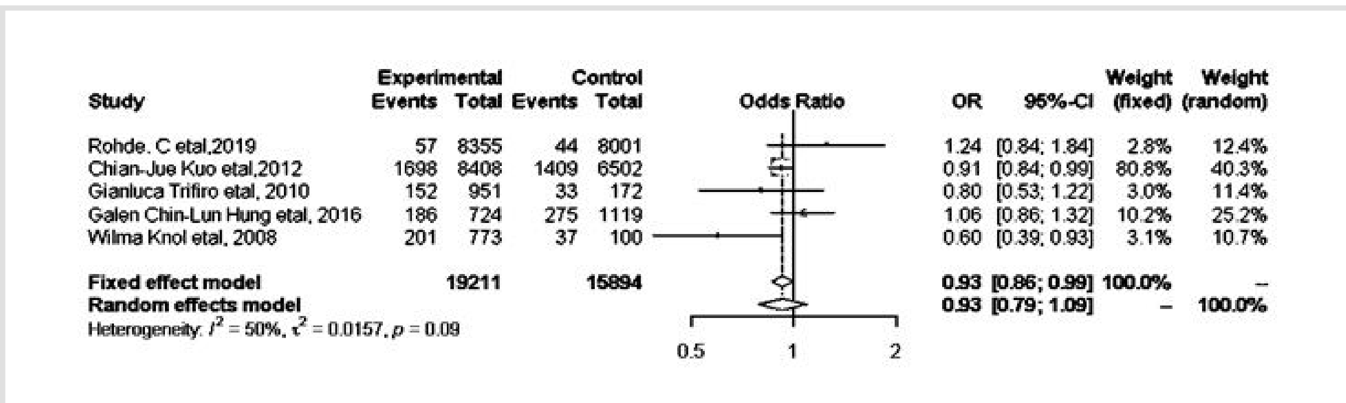

Figure 7. Risk of pneumonia with FGAs versus other psychotropic drug exposures.

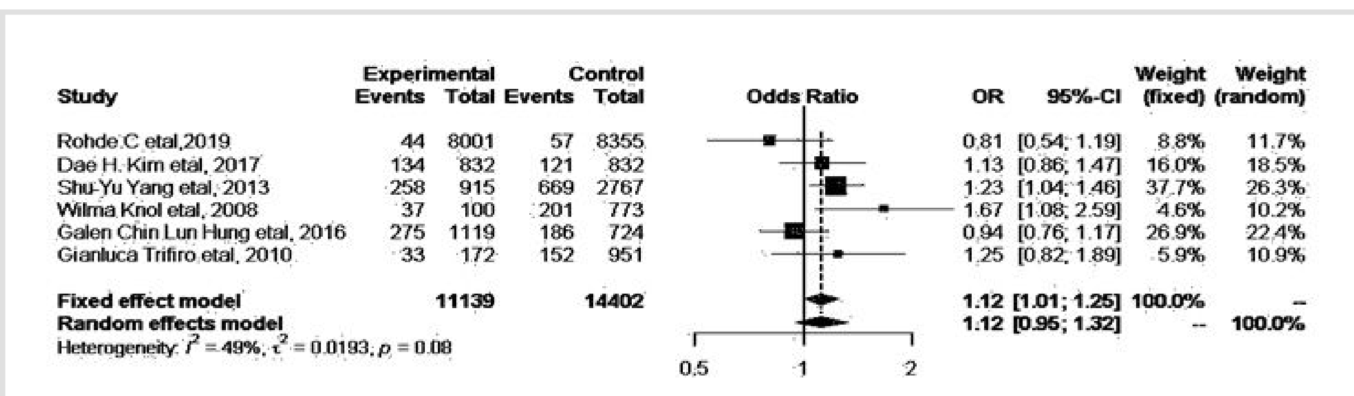

Figure 8. Risk of pneumonia with SGAs versus other psychotropic drug exposures.

following muscle relaxation, resulting in aspiration pneumonia (Pitts, 2014). Both human and animal studies have shown that opioids suppress the immune system by macrophage, lymphocytes inhibition, altered cytokine production, and impaired migration of neutrophils and macrophages (Hamina *et al*., 2019). Opioids also cause sedation, which increase the risk for aspiration and can also result in respiratory depression (Dublin *et al*., 2011). SSRI and SNRI may have an adverse effect on the immune cell function and its count, resulting in lower infection threshold, thereby increasing the risk of respiratory depression (Vozoris *et al* 2018). They also exhibit immunosuppressant effect which increases the risk of pneumonia (Rajamaki *et al*., 2020).

Clinical implications

AP, such as SGAs, BZD, opiates, and antidepressants, such as SSRI and SNRI, are associated with greater probability of

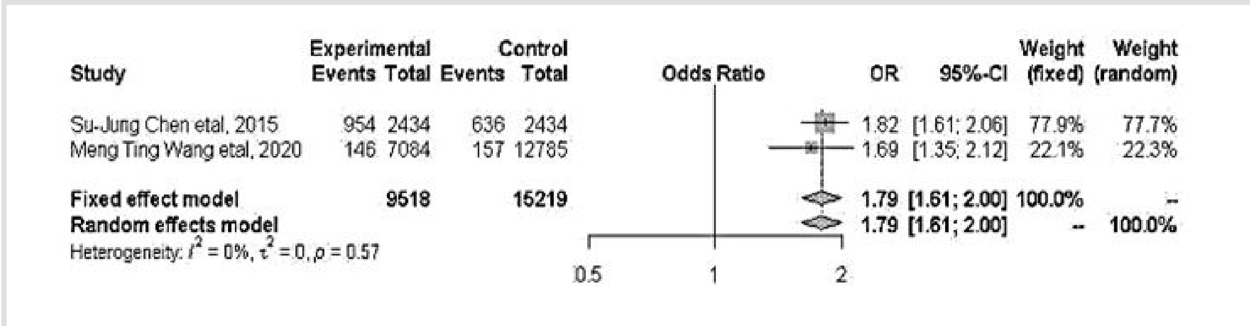

Figure 9. Risk of respiratory failure with psychotropic drugs exposure versus no exposure.

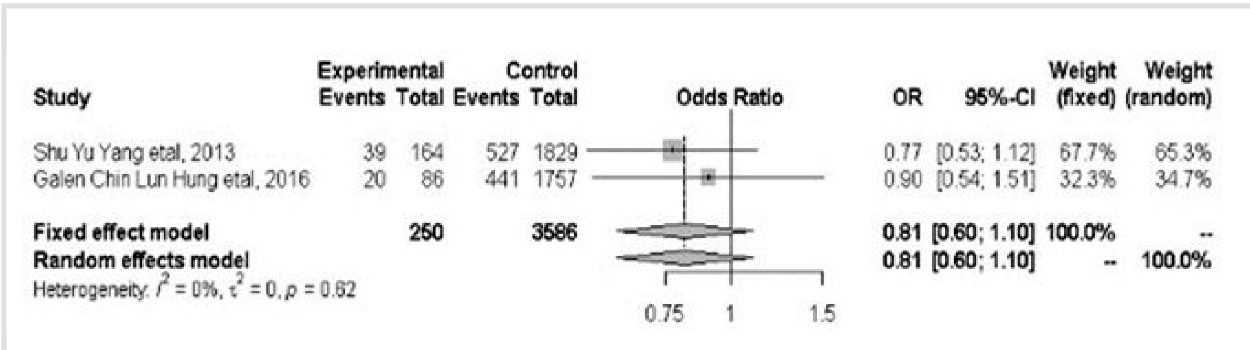

Figure 10. Chlorpromazine.

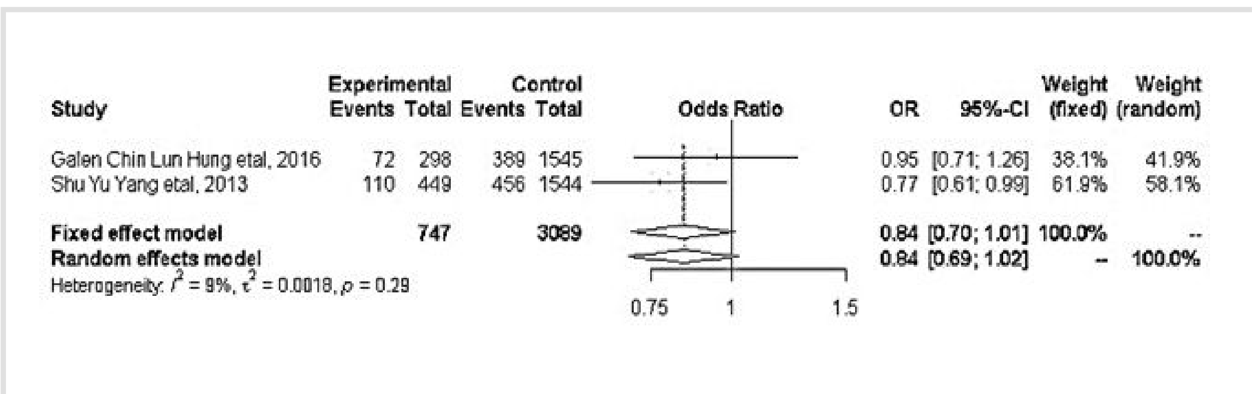

Figure 11. Sulpiride.

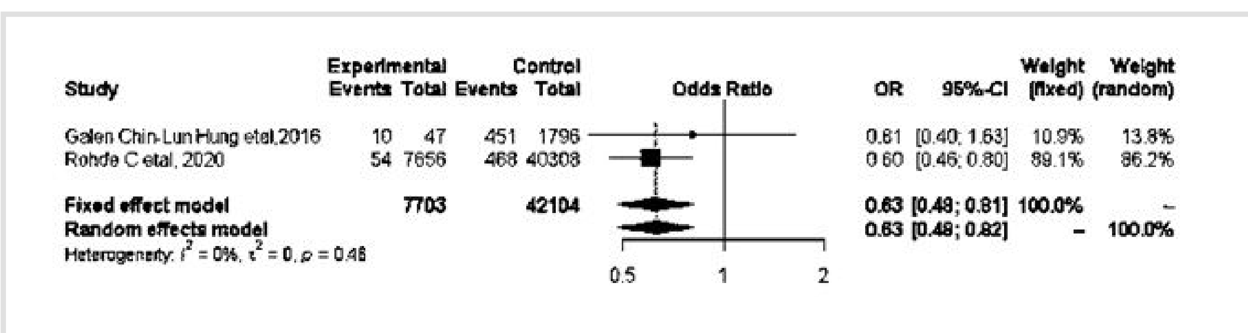

Figure 12. Aripiprazole.

developing pneumonia. Through our statistical subgroup analysis conducted, SGAs, such as risperidone, olanzapine, clozapine, quetiapine, zotepine, and amisulpride, have an increased risk of developing pneumonia; however, aripiprazole had a lower risk. Among the FGAs, haloperidol had an increased risk, whereas chlorpromazine and sulpiride had a lower risk of pneumonia. It was observed that the use of chlorpromazine among psychotropics was one of the most promising molecules showing inhibition of coronaviruses in the host cells (Plaze *et al*., 2020). Prescribed opioids, especially at doses which are high, and immunosuppressive opioids are associated with an increased risk of pneumonia (Edelman *et al*., 2019). A study (Cheng *et al*., 2018) reported that BZD has a dose-dependent association with the occurrence of pneumonia. BZRA, especially midazolam, was found to be related to an increased probability of occurrence of pneumonia, which reinforces the need for careful analysis of risk versus benefit before administration (Chen *et al*., 2017). SSRI and SNRI use was found to be associated with a statistically significant increase in the rate of respiratory-related morbidity and mortality, in a cohort of older adults with COPD (Vozoris *et al*., 2018). Respiratory infections, such as pneumonia, caused by AP and other psychotropic medications can cause unnecessary hospital admissions or prolong the duration of hospital stay in patients with psychiatric disorders (Stroup and Gray, 2018). In psychiatric patients with comorbid SARS-CoV-2 infection, aggravation of respiratory symptoms by use of antipsychotic medication can increase the need for ventilator support and risk of mortality (Wang *et al*., 2017a). Hence, it is vital to use AP appropriately in patients with SARS-CoV-2 infection and those at risk of other opportunistic infections (Ostuzzi *et al*., 2020). Our results demonstrate that FGAs should be the appropriate choice of AP in patients with schizophrenia with the following conditions: SARS-CoV-2 infection, prior history of recurrent pneumonia, immune status, and long-term use of corticosteroids.

CONCLUSION

FGAs are particularly associated with a lower risk for pneumonia compared to exposure to other psychotropic drugs, whereas SGAs are more significantly associated with the development of pneumonia with respect to other psychotropic drug exposure. Thus, FGAs are relatively safer when compared to SGAs and can be used as a first-line choice for the treatment of schizophrenia in patients with underlying respiratory comorbidities. The exposure to psychotropics can also contribute to the development of respiratory failure as well. Among various AP, SGAs, including risperidone, olanzapine, clozapine, quetiapine, zotepine, and amisulpride, significantly contribute to the development of pneumonia. However, aripiprazole has a lower risk. FGAs, such as haloperidol, have an increased risk of developing pneumonia following its usage, whereas chlorpromazine and sulpiride have a lower risk of pneumonia compared to other psychotropic drug usage. The study focuses on the need to abandon collective considerations about AP with respect to the risk of pneumonia and also shift the focus toward relative risks for the development of various respiratory outcomes and the risk associated with individual psychotropic drugs as well. The subgroup analysis performed in the study may help clinicians to practice the use of AP with minimal risk of respiratory deficits.

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AUTHORS' CONTRIBUTIONS

All the authors were involved in the literature review process, review designing, interpretation of the data and manuscript revision and shall be accountable for all the aspects of the study.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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