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Review

EEG changes in patients on antipsychotic therapy: A systematic review

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ABSTRACT

Objectives: The objective of the study was to characterize the electroencephalogram (EEG) changes associated with different antipsychotic medications based on the evidence from the literature.
Methods: A systematic search of the databases Medline, PsycINFO, and PubMed was conducted. The Preferred Items Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in the construction of this systematic review. Primary research articles that reported descriptive EEG results, included comparisons of subjects with and without antipsychotic therapy, and excluded patients with epilepsy were included in the analysis. The outcome was the presence of epileptiform discharges or slowing on EEG. We analyzed pooled data, where possible, from studies with a similar intervention and methodology.
Results: Fourteen articles reporting on a total of 665 patients were reviewed. Among the publications, clozapine was the drug most consistently accompanied by EEG slowing and epileptiform discharges, with an odds ratio of 16.9 (95% confidence intervals (CI): 5.4 to 53.2) and 6.2 (95% CI: 3.4 to 11.3), respectively in the analysis of pooled data. Only one study reported a significant increase in epileptiform discharges with phenothiazine antipsychotic therapy as a group, but the impact of individual drugs was not analyzed separately.
Conclusions: This systematic review suggests that, among antipsychotics, clozapine most frequently induces EEG slowing and epileptiform discharges. There remains limited data with respect to other individual antipsychotic agents and covariates including drug dose, plasma levels, dose adjustments, and treatment duration that influence EEG changes.

1. Introduction

Antipsychotic medications are traditionally used to treat psychotic disorders and bipolar affective disorder [1,2]. They are also prescribed as adjuncts in major depressive disorder, anxiety disorders, and managing behavioural symptoms in delirium and dementia [2–4].

Antipsychotics are categorised as typical (first generation)[1] or atypical (second generation).[2] Although poorly characterized, atypical antipsychotic effects are thought to generally reflect a complex interplay between serotonin and dopamine pathways [5]. Comparatively, typical antipsychotics primarily act as dopamine receptor antagonists, resulting in their greater association with extrapyramidal side effects [5]. However, antipsychotic medications lack pharmacological specificity and cause many other undesirable systemic sequelae, including autonomic changes, anticholinergic effects, cardiac dysrhythmias, and metabolic abnormalities [6,7]. Their use in older people is associated with falls, a heightened cardiovascular risk, and increased risk of death [8,9]. Antipsychotics are also reported to be associated with electroencephalographic (EEG) abnormalities [6].

Characterizing antipsychotic-associated EEG abnormalities is important as epileptiform discharges (ED) may indicate coexisting epilepsy, antipsychotic therapy-induced changes, or incidental findings [10]. The recognition of antipsychotic-associated abnormal EEG patterns can minimize the risk of misdiagnosis. Further, knowing which antipsychotics are likely to induce ED may help guide management decisions. For example, the finding of ED may restrict antipsychotic uptitration for fear of seizure provocation. More cautious approaches by clinicians may result in antipsychotic cessation or a trial of a prophylactic anticonvulsant although the place of primary prophylaxis is unclear [11].

Against this backdrop, this systematic review was conducted with the primary aim of characterizing EEG abnormalities following antipsychotic use. We hypothesized that antipsychotic drugs induce variable degrees of slowing and ED. Additionally, wherever possible, individual antipsychotic medications and antipsychotic class (typical and atypical) effects on EEG were compared. We also sought to evaluate the influence of drug dose, dose changes, and plasma concentrations on EEG changes.

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[1] Typical antipsychotics include, but are not limited to, chlorpromazine, fluphenazine, and haloperidol.
[2] Atypical antipsychotics include, but are not limited to, clozapine, olanzapine, quetiapine, and risperidone.

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2. Materials & methods

2.1. Search strategy

We performed a literature search utilizing the electronic databases Medline, PsycINFO, and PubMed. Key search words included "electroencephalography," "antipsychotic," "neuroleptic," and common antipsychotic drug names. Boolean operators were used to combine the search terms (Supplementary Table 1). Databases were searched from their inception to September 2017 for suitable publications. Titles and abstracts were screened to identify relevant articles. Reference lists of selected articles were screened for additional articles undetected by the primary search. We followed the Preferred Items Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in formulating the search strategy and this systematic review [12].

2.2. Eligibility criteria

We used the following inclusion criteria: primary research articles with (a) comparisons of subjects with and without antipsychotic therapy, (b) availability of descriptive EEG results, and (c) exclusion of patients with epilepsy. Articles based on animal experiments, quantitative EEG results, gray literature, and nonEnglish publications were excluded. To maximize data collection, no age restrictions were set. We followed the PRISMA guidelines in screening the titles and abstracts. The list of full-text articles was finalized in September 2017 (Fig. 1).

2.3. Data extraction

We used the Cochrane public health data extraction and assessment template to guide the development of a data extraction sheet [13]. Information collected included sex, age, patient cohort, duration of illness, exclusion criteria, study design, medication studied, duration of medication use, dosage, plasma drug levels, concomitant medication, EEG activation techniques (hyperventilation, intermittent photic stimulation, sleep deprivation), baseline and postmedication EEG reports, drug dose relationship with EEG, neuroimaging, seizure type, and seizure frequency. If data items were not reported or not applicable, the variable was recorded as not-specified or not-applicable, respectively. EEG descriptions "dysrhythmias" and "paroxysmal patterns" were considered abnormal, but nonspecific, and were not categorized as EEG slowing or ED. We classified the EEG slowing and epileptiform patterns according to the glossary of International Federation of Clinical Neurophysiology [14]. The EEG slowing was classified as focal, generalized, or not-specified (when details were not available). Epileptiform discharges were similarly classified (focal, generalized, not-specified).

2.4. Quality rating

Bias and quality assessment of all included studies was conducted using the Joanna Briggs critical appraisal tool for quasiexperimental studies (nonrandomised experimental studies) [15]. In brief, the tool facilitates critique of study quality in multiple domains including study conduct, methodology, the risk of bias, and results analysis. Two authors appraised the quality of included studies independently, and the final rating was concluded based on the consensus opinion in cases of discrepancy.

2.5. Synthesis of results and statistical analysis

We first present a narrative synthesis of the findings. This descriptive analysis examined all selected articles that fulfilled eligibility criteria. EEG data were populated and summarized into drug effects and drug-class effects. We compared the EEG abnormalities with and without antipsychotic therapy.

We pooled data from studies with a similar intervention, methodology, and outcome measurement. We calculated the odds ratio (OR) and the corresponding 95% confidence intervals (CI) for each study. The OR and the 95% CI of the pooled data were calculated using a random effects model. We employed chi-square and I^2 statistics to measure heterogeneity among the studies. The p values of <0.05 were considered significant whereas I^2 of 25%, 50%, and 75% were indicative of low, moderate,

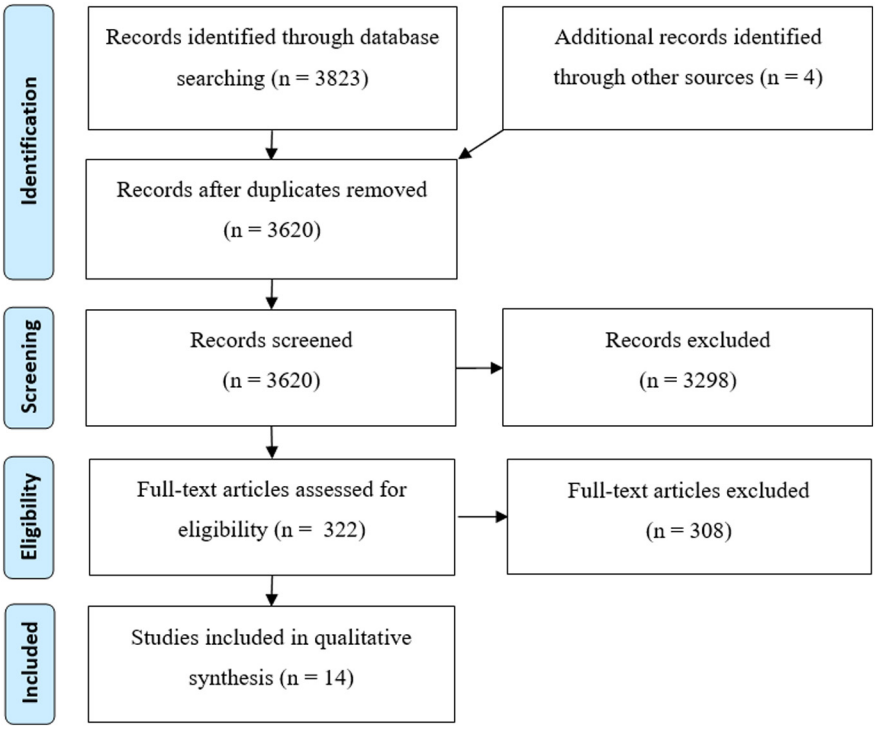

Fig. 1. PRISMA flow chart of study selection. PRISMA, Preferred Items Reporting for Systematic Reviews and Meta-Analyses. Excluded papers approximately consisted of nonEnglish studies (35%), animal studies (35%), quantitative EEG studies (20%), studies where patients with epilepsy were not definitely excluded (5%) and studies without comparator groups (5%).

and high heterogeneity, respectively [16]. We analyzed data using Review Manager (RevMan) software program (version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014).

3. Results

3.1. Bias and quality assessment

Fourteen studies conducted with quasiexperimental study designs fulfilled the eligibility criteria [17–30]. Interventions and outcomes of measures were clearly defined. By nature of design (pre- and postintervention), subjects remained the same without any randomisation. Further, all studies except one lacked an independent control group [17,18,20–30]. Methodological flaws, including occasional concurrent psychoactive medication use in some studies, may have affected the reliability of results [19,21,22,24–26,30]. The follow-up, owing to acute medical illness or medication adverse effects, was incomplete in some studies [21,23,25,26,30]. However, in these studies, patients excluded or lost to follow-up were omitted from analysis ensuring that all subjects were compared for pre- versus postintervention outcomes. The overall quality assessment of all included studies is summarized in Supplementary Table 2.

3.2. Study and patient population characteristics

A total of 14 studies evaluating typical and atypical antipsychotic effects on EEG, collectively consisting of 665 patients, were included in the final analysis [17–30]. Most studies were conducted before the year 2000 [17,18,22–25,27,30] with studies analyzing typical antipsychotics being the oldest [17,18]. The cohort of patients included in the studies was mostly diagnosed with mental health disorders, usually schizophrenia [17–23,25–30]. There was an approximately equal representation of males and females. Patients were mostly of young or middle age, with only one study analyzing antipsychotic use in older adults, averaging 73 years [24]. This particular study evaluated the EEG effects of low-dose clozapine in patients with Parkinson's disease, some of whom had coexisting dementia [24]. Comorbidities were not described in detail in any study. Eight studies evaluated clozapine [20–27], two olanzapine [28,29], and one each of chlorpromazine [17] and remoxipride [30]. One study analyzed patients on typical antipsychotics (phenothiazine group) [18], whereas a large cohort of patients on typical or atypical antipsychotics was evaluated in the other study included in our review [19]. Covariates such as drug dose, plasma concentrations, drug dose relationships with EEG changes, and seizure frequency were inconsistently reported among all included studies. The use of concomitant psychoactive medications, including mood stabilisers and benzodiazepines, was only occasionally reported. Polypharmacy and drug–drug interactions were not directly referenced to in any of the included studies (Table 1).

3.3. Analysis of EEG abnormalities

3.3.1. Analysis of pooled data

3.3.1.1. Epileptiform EEG discharges. Pooling of data was feasible only for studies involving clozapine, an atypical antipsychotic. Eight publications on clozapine therapy comprising 229 patients were included in this review [20–27]. The forest plot summarizes our results (Fig. 2). The OR of epileptiform abnormalities following clozapine therapy was 6.2 (95% CI: 3.4 to 11.3). This finding suggests that clozapine therapy increased the odds of ED occurrence on EEG by six times. The included studies had very low heterogeneity ($I^2 = 0\%$). All but one study showed

Table 1
General summary of all included studies [17–30].

Study	Gender	Mean age (SD) (range)	Patient cohort	The average illness duration (years) (SD) (range)	Total number	Drug	Mean dosage (mg/d) (SD) (range)	Mean plasma level (μg/L) (SD) (range)	Psychoactive cotherapy?	Normal baseline EEG?	Dose related increase in EEG changes
Centorrino et al. (2002)	148M, 145F	35.6 (15.7) (13-82)	SSD, BPAD, MDD	NS	293	FGA + SGA	[a]	NS	Y	N	NS
Chung et al. (2002)	35M, 15F	31.6 (7.8) (NS)	SCZ	NS	50	CLZ	364.8 (121.7) (100-625)	NS	NS	Y	Y
Degner et al. (2011)	15M, 7F	44.8 (15.2) (18-69)	SCZ	NS	22	OLZ	17.5 (8.6) (5–35)	34.2 (26.9) (5-111)	N	Y	Y
Jorgensen et al. (1957)	20M, 0F	NS (NS) (17-59)	SCZ	NS	20	CPZ	NS (NS) (300-1500)	NS	NS	N	NS
Kikuchi et al. (2014)	8M, 18F, 2NS	37 (NS) (NS)	SCZ	A—15.4 (10.4) (NS); B—6.9 (5.3) (NS)[b]	26	CLZ	A—378.1 (179.8) (NS); B—305.0 (131.7) (125-600)	NS	Y	Y	N
Lindstrom et al. (1985)	7M, 3F	32.0 (NS) (19-42)	SCZ	9 (NS) (1-20)	9	REM	150-300 (NS) (NS)	NS	Y	Y	NS
Malow et al. (1994)	7M, 3F	30.3 (5.3) (20-41)	SCZ	NS	10	CLZ	490.0 (222.3) (200-900)	NS	Y	Y	NS
Mozes et al. (2003)	6M, 3F	12.5 (1.1) (NS)	SCZ	2.8 (0.5) (2-5)	9	OLZ	15.6 (4.6) (10-20)	NS	NS	Y	NS
Neil et al. (1978)	NS	NS	SSD	NS	83	PTZ	NS	NS	NS	N	N
Neufeld et al. (1996)	10M, 10F	73 (9.7) (48-85)	PD, dementia	6.7 (6.50) (2-20)	20	CLZ	31.8 (20.7) (6.25-75)	NS	Y	N	NS
Risby et al. (1995)	19M, 7F	35.2 (6.7) (22-55)	SSD	NS	16	CLZ	373.4 (95.8) (200-525)	NS	Y	N	N
Shrivastava et al. (2014)	66M, 14F, 52NS	33.4 (7.1) (NS)	SCZ	2.6 (0.7) (NS)	80	CLZ	265 (NS) (NS)	NS	Y	N	Y
Tiihonen et al. (1991)	NS	NS	SCZ	NS	16	CLZ	512 (NS) (300-700)	NS	NS	N	NS
Treves & Neufeld (1996)	7M, 8F	35 (14) (20-50)	SCZ	7 (4) (3-15)	11	CLZ	300 (fixed dose)	NS	NS	Y	NS

Abbreviations—*CLZ*: clozapine, *CPZ*: chlorpromazine, BPAD: bipolar affective disorder, *FGA* & *SGA*: first-generation (typical) and second-generation (atypical) antipsychotics, *MDD*: major depressive disorder, *N*: no, *NS*: not-specified, *OLZ*: olanzapine, *PD*: Parkinson's disease, *PTZ*: phenothiazines, *REM*: remoxipride, *SCZ*: schizophrenia, *SSD*: schizophrenia spectrum disorders, *Y*: yes.

[a] Expressed in chlorpromazine equivalents.

[b] In this study, group A and group B included patients with normal EEG and abnormal EEG, respectively.

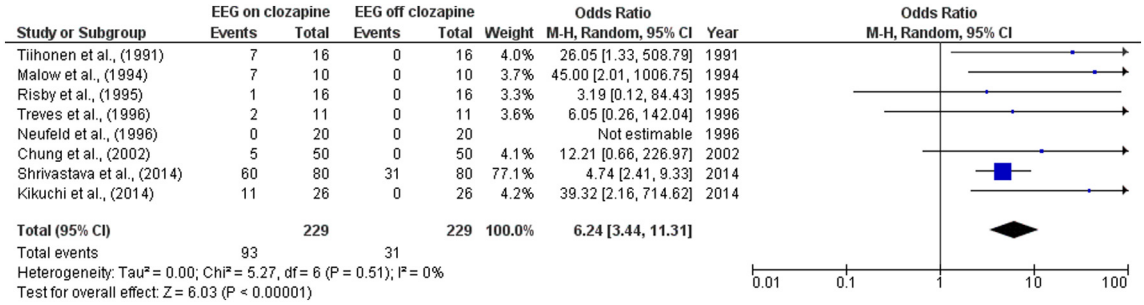

Fig. 2. Forest plot comparing EEG ED before and after clozapine therapy among included studies. M-H, Mantel–Haenszel.

an increase in ED after clozapine treatment [20–23,25–27]. Subtypes of ED were poorly described. Only two studies presented a breakdown of ED type (generalized versus focal) [22,23]. One of these studies demonstrated an increase in both focal and generalized ED with clozapine therapy (Table 2) [23]. Two patients exhibited photoparoxysmal response (PPR) on clozapine [22]. The average daily clozapine dose, dose ranges, and dose relationships with EEG abnormalities among studies are summarized in Table 1. Plasma clozapine levels were not reported.

3.3.1.2. Nonepileptiform abnormalities (EEG slowing). Similar to the analysis of epileptiform abnormalities, data pooling was feasible only in eight studies involving clozapine therapy, and the findings are highlighted in the forest plot (Fig. 3). The OR was 16.9 (95% CI 5.4 to 53.2). The I^2 was 55% suggesting moderate heterogeneity among the studies. EEG slowing, when detailed, was typically generalized (Table 3) [22,23,25,27].

3.3.2. Other individual antipsychotics and EEG effects

3.3.2.1. Typical antipsychotics. Neil et al. [18] reported EEG changes in a cohort of patients on various phenothiazines where perphenazine was the most frequently used drug (in 62). Significant increases in ED (focal and generalized) from 17.9% (baseline) to 42.6% (on medication) and slowing from 16.8% to 28.7% were found in the cohort ($p < 0.001$ & 0.04, respectively). However, the individual drug effects are not reported separately in this paper.

Table 2
Summary of EEG ED before and after antipsychotic exposure of all included studies [17–30].
See Supplementary Table 3 for further detail.

Study	Number of subjects	Drug	Total ED		Generalized ED		Focal ED		Seizures, n (%)
			Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	
Centorrino et al. (2002)	293	FGA + SGA	0	2.7%	0	0	0	0	NS
Chung et al. (2002)	50	CLZ	0	10%	0	0	0	0	2 (4%)
Degner et al. (2011)	22	OLZ	0	4.5%	0	0	0	0	0 (0%)
Jorgensen et al. (1957)	20	CPZ	10%	15%[a]	0	0	0	0	1 (5%)
Kikuchi et al. (2014)	26	CLZ	0	42.3%	0	0	0	0	6 (23.1%)
Lindstrom et al. (1985)	9	REM	0	0	0	0	0	0	NS
Malow et al. (1994)	10	CLZ	0	70%[b]	0	70%	0	0	7 (70%)
Mozes et al. (2003)	9	OLZ	0	0	0	0	0	0	NS
Neil et al. (1978)	83	PTZ	17.9%	42.6%	13.7%	28.7%	4.2%	14%	NS
Neufeld et al. (1996)	20	CLZ	0	0	0	0	0	0	0 (0%)
Risby et al. (1995)	16	CLZ	0	6.3%	0	0	0	0	0 (0%)
Shrivastava et al. (2014)	80	CLZ	38.8%	75%	0	0	0	0	NS
Tiihonen et al. (1991)	16	CLZ	0	43.8%	0	0	0	0	NS
Treves & Neufeld (1996)	11	CLZ	0	18.2%	0	9.1%	0	9.1%	0 (0%)

The total ED may not necessarily be equal to the sum of focal ED and generalized ED as in some studies the ED classification is not specified. Abbreviations—*CLZ*: clozapine, *CPZ*: chlorpromazine, *ED*: epileptiform discharges, *FGA* & *SGA*: first-generation (typical) and second-generation (atypical) antipsychotics, *n*: number, *NS*: not-specified, *OLZ*: olanzapine, *PPR*: photoparoxysmal response, *PTZ*: phenothiazines, *REM*: remoxipride.

[a] The study by Jorgensen and Wulff [17] reports 3 patients with PPR.

[b] The study by Malow et al. [22] reports 2 patients with PPR.

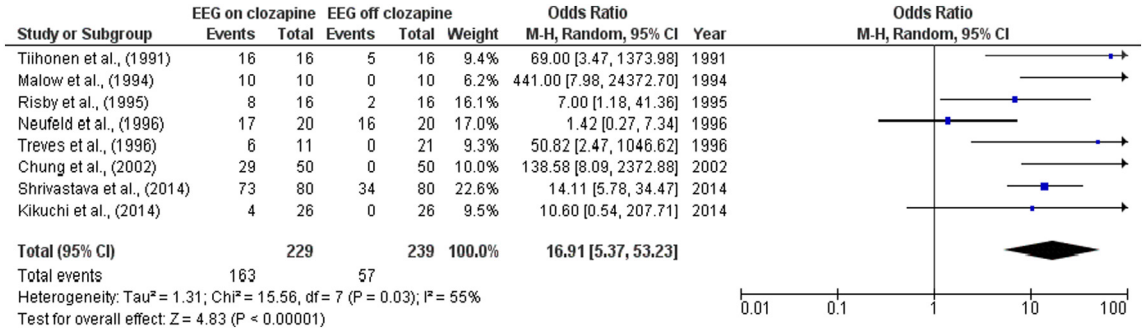

Fig. 3. Forest plot comparing EEG slowing before and after clozapine therapy among included studies. M–H, Mantel–Haenszel.

Table 3
Summary of EEG slowing before and after antipsychotic exposure of all included studies [17–30].
See Supplementary Table 3 for further detail.

Study	Number of subjects	Drug	Total slowing		Generalized slowing		Focal slowing		Mixed slowing		NI[a] (abn)[b]	NE[a] (abn)[b]
			Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment		
Centorrino et al. (2002)	293	FGA + SGA	1%	8.2%[c]	0	0	0	0	0	0	Y (Y)	NS
Chung et al. (2002)	50	CLZ	0	58%	0	0	0	0	0	0	NS	NS
Degner et al. (2011)	22	OLZ	0	18.2%	0	4.5%	0	13.6%	0	0	Y (Y)	Y (NS)
Jorgensen et al. (1957)	20	CPZ	10%	40%	0	0	0	0	0	0	NS	NS
Kikuchi et al. (2014)	26	CLZ	0	15.4%	0	0	0	0	0	0	NS	NS
Lindstrom et al. (1985)	9	REM	0	0	0	0	0	0	0	0	NS	NS
Malow et al. (1994)	10	CLZ	0	100%	0	100%	0	0	0	0	Y (Y)	NS
Mozes et al. (2003)	9	OLZ	0	0	0	0	0	0	0	0	NS	Y (NS)
Neil et al. (1978)	83	PTZ	16.8%	28.7%	12.6%	20.9%	1.1%	2.3%	0	0	NS	Y (N)
Neufeld et al. (1996)	20	CLZ	80%	85%	50%	50%	5%	5%	25%	30%	Y (NS)	Y (NS)
Risby et al. (1995)	16	CLZ	12.5%	50%	0	18.8%	12.5%	12.5%	0	0	NS	NS
Shrivastava et al. (2014)	80	CLZ	42.5%	91.3%	0	0	0	0	0	0	NS	NS
Tiihonen et al. (1991)	16	CLZ	31.3%	100%	0	25%	0	0	0	0	NS	Y (NS)
Treves & Neufeld (1996)	11	CLZ	0	54.5%	0	54.5%	0	0	0	0	NS	NS

The sum of individual categories may not necessarily be equal to totals due to multiple EEG abnormalities in tracings for some patients and the lack of details on the type of slowing (focal versus generalized) among some studies. Abbreviations—*CLZ*: clozapine, *CPZ*: chlorpromazine, *FGA* & *SGA*: first-generation (typical) and second-generation (atypical) antipsychotics, *N*: no, *NS*: not-specified, *OLZ*: olanzapine, *PTZ*: phenothiazines, *REM*: remoxipride, *Y*: yes.

[a] Did studies perform baseline neuroimaging (NI) or neurological examinations (NE) among study participants?

[b] Were baseline abnormal neuroimaging (NI) or neurological examinations (NE) an exclusion criteria among included studies?

[c] The study by Centorrino et al. [19] reports an additional undifferentiated category of EEG slowing (not-specified) and ED (not-specified). In this category, pretreatment and posttreatment percentages are 0.3% and 8.2%.

One study, comprising 20 patients, evaluated chlorpromazine [17]. There was no significant increase in epileptiform EEG abnormalities with treatment ($p = 0.67$). Photoparoxysmal response was evoked in 3 patients [17]. Two patients had baseline EEG slowing with a significant increase to eight following chlorpromazine therapy ($p = 0.04$) [17]. Another study involving 14 patients did not find a significant increase in ED ($p = 0.3$) [19]. Dosing details are seen in Table 1.

A small number of patients on mesoridazine [3], fluphenazine [18], and thioridazine [23] did not demonstrate ED in their EEG. Only one patient each had ED in two groups of patients on trifluoperazine (11 subjects) and perphenazine (70 subjects) [19].

Only a single study included in our review provides data on other typical antipsychotics [19]. No patient on haloperidol (55 subjects) and loxapine (4 subjects) had ED in the EEG. There were nine patients on thiothixene, and only one demonstrated ED.

3.3.2.2. Atypical antipsychotics. Three studies, comprising a total of 44 patients on olanzapine, reported inconsistent results [19,28,29]. One study did not find EEG changes (ED or slowing) after olanzapine exposure [29]. Other studies reported a 4.5% and 7.7% increase in ED which were not statistically significant ($p = 0.5$ & 0.3) [19,28]. One study found an insignificant increase of 18.2% in slowing with olanzapine therapy ($p = 0.1$) [28]. The average daily olanzapine dose, dose ranges, and dose relationships with EEG abnormalities among studies are summarized in Table 1.

Only one study evaluated risperidone in 25 patients versus 30 controls not on any antipsychotic therapy [19]. Epileptiform discharges increased from 0% (control) to 4%, but the difference was not significant ($p = 0.5$). The same paper reported on five patients on quetiapine, and none had ED. Remoxipride, an atypical antipsychotic which is mostly discontinued, did not cause any EEG abnormalities in the single study included in this review [30].

3.3.2.3. Typical versus atypical antipsychotics. Only one study evaluated the impact of typical versus atypical antipsychotics as a group [19]. With typical antipsychotic therapy, ED abnormality increased from 0% (baseline) to 1.9% ($p = 0.6$), whereas with atypical antipsychotics, the increase was from 0% to 5.1% ($p = 0.3$). There was no significant difference between typical and atypical antipsychotic drugs as groups ($p = 0.1$).

3.4. Antipsychotic dose and EEG trends

In this review, a few studies evaluated the relationship between antipsychotic dose and EEG changes. One study reported a significantly higher average dosage of olanzapine (24.4 mg/d versus 12.7 mg/d,

$p < 0.001$) in patients with EEG abnormalities comprising slowing and ED [28]. Clozapine studies were conflicting; two studies reported a dose-dependent relationship with EEG abnormalities [20,26] and two did not [21,25]. Among the positive studies, one reported a significant correlation between a higher clozapine dose and EEG slowing ($r = 0.27$, $p = 0.04$) [26]. The other reported the frequency of EEG abnormalities (nonepileptiform and epileptiform) in those receiving ≤300 mg/d and >300 mg/d of clozapine as 42.1% and 74.2%, respectively ($p = 0.023$) [20].

3.5. Antipsychotic use and seizure occurrence

Though not our main objective, we also studied the incidence of seizures among the patient cohorts included in this review. Eight studies commented on seizure onset following antipsychotic treatment [17,20–25,28]. Six of these studies evaluated clozapine [20–25], one studied chlorpromazine [17], and one olanzapine [28].

Overall, seizure occurrence ranged from 0 to 70% among the studies. A total of 16 patients experienced seizures during antipsychotic therapy; one patient treated with chlorpromazine had a generalized tonic–clonic seizure (GTCS) while the remaining 15 experienced myoclonus or, less often, GTCS during clozapine treatment (Supplementary Table 4). There were no seizure reports with olanzapine therapy.

4. Discussion

This review of 14 studies evaluating the characteristics of EEG changes associated with antipsychotic use shows that nonepileptiform (EEG slowing) and epileptiform EEG patterns are significantly associated with the use of clozapine. Both focal and generalized ED were observed following clozapine therapy. There was limited data on other antipsychotics. Only one study reported a significant increase in ED with phenothiazine therapy as a group, but the impact of individual drugs was not specified separately [18].

4.1. Antipsychotic use and ED

Introduced in the 1950s, many typical antipsychotics are still prescribed in clinical practice, though infrequently. Although no firm conclusions can be drawn as only a few studies are available, data suggest a higher risk of inducing epileptiform EEG abnormalities with phenothiazine compared with nonphenothiazine typical antipsychotics.

Individually, clozapine seems to most consistently induce ED compared with chlorpromazine and olanzapine. Three studies included in our analysis did not find a significant increase in ED with olanzapine therapy [19,28,29]. The contrast between clozapine and olanzapine is intriguing given that olanzapine's chemical structure and pharmacological profile (high 5-HT_{2A}/D_2 ratio) resembles that of clozapine [5]. The contrast between clozapine and olanzapine posttreatment changes may reflect the smaller body of literature with olanzapine. Centorrino et al. [19] suggest haloperidol and quetiapine may not be associated with ED, although the limitations of a single study should be recognized. The distribution of ED (focal or generalized) was characterized poorly. Among the three studies detailing ED distribution, two reported a trend toward both focal and generalized ED following antipsychotic use [18,23] and one a trend toward generalized ED [22].

Generalized PPR is typically seen with underlying genetic generalized epilepsy [31]. Studies included in this review inconsistently reported EEG methodology, particularly the use of intermittent photic stimulation. The PPR was evoked in three patients taking chlorpromazine [17] and in two patients taking clozapine [22]. One study of clozapine may suggest a dose relationship given PPR regression with dose deescalation [22].

4.2. Antipsychotic use and EEG slowing

A trend toward EEG slowing was seen with both classes of antipsychotics. In relation to individual antipsychotics, the highest posttreatment increase in EEG slowing was seen with clozapine followed by chlorpromazine. Clozapine was strongly associated with EEG slowing, demonstrating an OR of 16.9.

One study on olanzapine, which excluded subjects with abnormal magnetic resonance brain imaging, showed a subtle nonsignificant trend toward focal slowing [28]. Contrastingly, generalized EEG slowing was seen with clozapine use [22–25,27], including 2 studies [24,25] reporting a wider distribution of slowing on EEG in some patients with preexisting focal slowing.

Compared with focal EEG slowing which indicates regional brain dysfunction, the finding of generalized EEG slowing typically implies an underlying encephalopathy indicative of widespread brain dysfunction [32,33]. Although our findings suggest that antipsychotics may produce focal or generalized slowing on EEG, or provoke a greater breadth of brain involvement in patients with preexisting focal slowing, it must be recognized that most studies did not report baseline neurological examination or neuroimaging. Additionally, the clinical consequence of these EEG changes following antipsychotic therapy is uncertain.

4.3. Antipsychotic variables (dose, dose adjustments, and plasma concentrations) and EEG trends

There are conflicting results regarding the relationship between antipsychotic dose and EEG changes. No studies commented on the timing of EEG changes with antipsychotic dose adjustments. A meta-analysis by Varma et al. [34] of clozapine-induced EEG changes in patients with and without epilepsy highlighted an apparent clozapine dose relationship, with an 8% rise in abnormal (nonepileptiform and epileptiform) EEG findings with every 100-mg dose increment.

Expert consensus guidelines recommend antipsychotic therapeutic drug monitoring where available as oral drug dosing regimens may have variable pharmacokinetics depending on patient characteristics [35]. Guidelines support therapeutic drug monitoring for patients older than 65 years, with multimorbidity, and those on multiple medications at risk of drug–drug interactions [35]. In this review, only one study reported plasma levels, stating that olanzapine plasma levels were not associated with EEG abnormalities [28]. None of the studies reported clozapine plasma levels, whereas a meta-analysis by Varma et al. [34] found that every 100-μg/L increase in clozapine levels corresponded with a 12% increase in abnormal EEGs. Overall, in our review, there is insufficient data to speculate on whether antipsychotic plasma concentrations are associated with EEG changes.

4.4. The relationship between EEG changes and seizure onset

The emergence of ED may raise uncertainty in the clinician's mind regarding an impending seizure. However, the relationship between ED and seizures is uncertain, and the seizure risk needs to be evaluated in the clinical context [36–38].

The unclear association between ED and onset of seizures is illustrated by four papers included in our study that reported ED associated with clozapine [20,23,25] and olanzapine [28] use are frequently nonspecific and do not necessarily indicate impending seizures. Three other studies on clozapine did not directly address this issue, but uncertainty regarding the clinical significance of ED was noted [21,22,24].

4.5. Clinical implications

The presence of interictal ED in the EEG of a patient on antipsychotic therapy should be interpreted very carefully in the clinical context as ED may be due to antipsychotic treatment, comorbid epilepsy, or coincidence [10].

Although epileptiform EEG abnormalities help confirm the diagnosis of epilepsy and classify epilepsy type, this study suggests that antipsychotics may induce similar findings in people without underlying epilepsy. Failure to recognize that ED can be induced by antipsychotics may lead to epilepsy misdiagnosis and exposure to unnecessary long-term anticonvulsant therapy with potential adverse effects [10].

However, the possibility of coexisting epilepsy in an individual prescribed with antipsychotic therapy should be also carefully explored. Further investigations such as video-EEG monitoring may be warranted in inconclusive cases. Delineating the true cause of ED is both important and complicated, and so requires careful interpretation in the clinical context.

A pertinent question in this population is whether the presence of ED in EEG heralds seizures and prophylactic antiepileptic drug therapy is indicated. Our study did not find sufficient data to explore this relationship. In view of the ambiguity surrounding whether ED heralds seizures, well-designed prospective studies are needed to answer the practical question of whether prophylactic anticonvulsant therapy is indicated. In the interim, antipsychotics should be used judiciously in patients with ED on EEG or at high risk of seizures. Alternatively, if antipsychotics are required, those drugs that have little or no association with ED should be considered.

Further, the treatment of seizures while on antipsychotics requires thoughtful deliberation. Seizures in this population may be acute symptomatic or unprovoked if the subject has underlying epilepsy. Treatment duration and seizure recurrence risk in this cohort remains unclear, and also requires further studies.

4.6. Limitations of the literature

Among the large body of literature screened, only a small number of studies detailed baseline EEGs or provided controls in order to accurately characterize a particular antipsychotic's effect. Some studies in this review included patients with abnormal EEGs before commencing antipsychotic therapy. This remains problematic as EEGs may be abnormal in asymptomatic individuals, or in the setting of neurological or psychiatric illness [10]. Further, schizophrenia has been shown to be associated with sleep abnormalities including insomnia, circadian rhythm disorder, poor sleep efficiency, slow wave sleep deficit, and increased rapid eye movement sleep density [39,40]. These sleep disturbances are likely to have an effect on EEG recordings, in particular, sleep activation during the EEG, and the EEG outcomes.

Descriptions of EEGs, whether preexisting or after antipsychotic therapy, were occasionally vague or used terms (e.g., 'dysrhythmia') that are now discouraged due to their ambiguity. Further, there was variability in EEG classifications and subtyping between studies. Occasionally, studies used graded EEG severity scales with overlapping findings.

It is well-known that the yield of epileptiform abnormalities in the EEG depends on several intrinsic and extrinsic variables including the length and time of the recording [41,42]. Among studies included in our analysis, there was a lack of technical detailing of EEG recording, with limited information regarding the duration of recording and activation techniques (sleep deprivation, hyperventilation, and photic stimulation). Even among patients with epilepsy, the diagnostic yield of a single EEG is 55% [42]. Though there are no specific studies, it is possible those variables also impact the EEG outcomes among patients on antipsychotics. Hence, results based on two EEGs, before and after therapy, may not be completely reliable. This is a major limitation in the literature. Furthermore, in old studies, EEGs were recorded with fewer channels. This is another limitation as technical factors have a significant impact on the EEG yield [43].

Additionally, the timing of the EEG in relation to the medication administration and seizures is likely to impact the outcome. This information is largely lacking in the included studies and only a few studies attempted to standardize EEG recording intervals by repeating EEGs after specified time periods [18,21,30] or specific drug doses [23]. This impact can be minimized by the use of standardized EEG recording protocols prospectively.

Older studies were prone to methodological flaws where patients were coprescribed psychoactive medications with a potential to cause EEG changes. Some studies transformed different antipsychotic doses into "chlorpromazine equivalents" [19]. This reporting strategy makes dose comparisons difficult. Studies variably commented on the patient's baseline neurological examination and neuroimaging. In their absence, appraising the type and distribution of EEG abnormalities is imperfect. Analyzed papers used quasiexperimental study designs. Nonrandomisation and lacking control groups affects study quality and validity.

There was variable detailing of antipsychotic doses, plasma concentrations, the temporal relationship of dose adjustments, and psychoactive cotherapy. The vast majority of studies included in this review involve clozapine. Hence, we emphasize that the results cannot be generalized for all antipsychotics. We also emphasize the potential for publication bias for studies showing significant differences. Seizure occurrence was uncommonly recorded, and when collected, data was not adequately detailed. The descriptions on seizure semiology were inadequate.

The majority of available literature mostly studied patients diagnosed with schizophrenia spectrum disorders who were generally adolescent or middle aged. Although the main users of antipsychotics are patients with mental illness, indications in other patient populations are equally pertinent. For example, in older adults, antipsychotics are used in the behavioural management of patients suffering from delirium or dementia. In our analysis, there was only one study of older adults appraising an uncommonly used antipsychotic in this cohort [24]. There were limited studies assessing more commonly used antipsychotics such as haloperidol, risperidone, and quetiapine in older adults.

We applied strict inclusion and exclusion criteria to select studies for our analysis. However, the adherence to these criteria between the studies may have been variable. In particular, the exclusion of patients

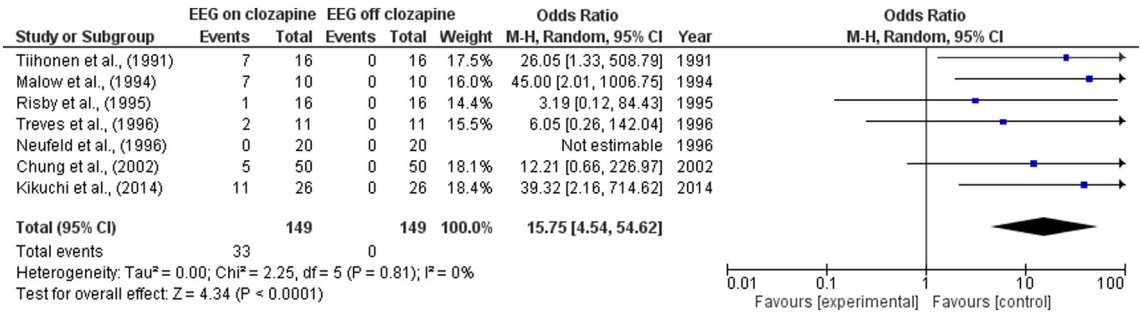

Fig. 4. Forest plot comparing EEG ED before and after clozapine therapy among included studies excluding Shrivastava et al. [26]. M–H, Mantel–Haenszel.

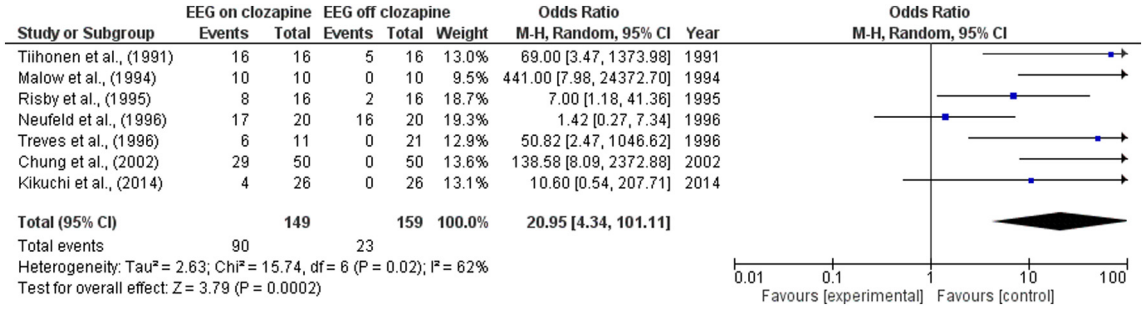

Fig. 5. Forest plot comparing EEG slowing before and after clozapine therapy among included studies excluding Shrivastava et al.[26]. M–H, Mantel–Haenszel.

with epilepsy can be challenging which may need expert assessment. We highlight that the paper by Shrivastava et al. [26] involving patients presenting with the first episode of psychosis reports an unusually high percentage of EEGs with EDs in the pretreatment phase. We included this paper in our analysis as it fulfilled all the eligibility criteria, particularly the exclusion of subjects with epilepsy. However, it may be possible that authors may have inadvertently included patients with epilepsy in their cohort resulting in this high number of abnormal EEGs. We have reanalyzed data with the exclusion of this particular study, and the new analysis did not change our conclusions. The results still demonstrate significantly high OR for both ED and slowing after clozapine therapy (Figs. 4, 5). Hence, we have opted to keep this study in the original analysis to ensure strict adherence to our inclusion and exclusion criteria while highlighting this potential pitfall.

4.7. Gaps in current knowledge and future directions

Numerous antipsychotics are currently available in clinical practice. There is still a lack of large-scale, prospective studies comprehensively investigating antipsychotic-associated EEG abnormalities and seizures. Covariates such as drug dose, plasma levels, dose adjustments, and duration of treatment that contribute to EEG alterations are not well-defined. Most studies have been limited to psychiatric populations.

Large-scale, prospective, randomised, studies with rigorous methodology assessing a broad range of antipsychotics with a detailed evaluation of dosing variables, EEG effects, and association with seizures are essential to understand the complex relationship among antipsychotics, EEG abnormalities, and seizures. Using standardized EEG recording protocols and terminology in reporting is essential to ensure homogeneity among studies. In the context of an aging population, antipsychotic use can be anticipated to increase. Therefore, further studies evaluating antipsychotic effects on EEG in more diverse patient populations, including older adults, are desirable.

The clinical implications of epileptiform EEG abnormalities in the context of antipsychotic use raise treatment uncertainties including impending seizure risk and further treatment dilemmas such as whether to reduce the antipsychotic dose, use alternative antipsychotics, or commence anticonvulsants. These treatment challenges require further research.

5. Conclusion

Some antipsychotics may generate EEG abnormalities including slowing and ED. Detailed EEG data are lacking with most antipsychotics except clozapine. Within the limited dataset, clozapine is likely to be associated with a significant risk of inducing ED and slowing. It remains unclear whether ED correlate with seizure generation.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.02.005.

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Declarations of interest

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