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Review article

Antipsychotic treatment failure in patients with psychosis and co-morbid cannabis use: A systematic review

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ABSTRACT

Whilst the effects of cannabis preceding psychosis onset are well established, an effect post-onset is less clear. Emerging evidence suggests that cannabis use is associated with increased relapse outcomes possibly because of determinants, antipsychotic treatment failure and medication adherence, that are not mutually exclusive. Due to the paucity of literature on antipsychotic treatment failure an association with cannabis remains conjectural. This review sought to summarise current evidence regarding the effect of cannabis use on antipsychotic treatment failure among users and non-users with psychosis. Ovid databases (Embase, Journals@Ovid Full Text, OvidMEDLINE® In-Process and Other Non-Indexed Citations and PsycINFO) were searched to identify relevant articles. Seven articles met eligibility criteria. Cannabis use was associated with the following deleterious outcomes increased: odds of non-remission, prescription of unique antipsychotic medications, cumulative prescription of Clozapine and poor treatment trajectories. One study reported similar life-time, but lower past-year, rates of cannabis use in those prescribed Clozapine. Another study reported differences between groups for chlorpromazine equivalent doses for long-term Olanzapine prescription. Improved methodologies are warranted due to a lack of well-designed prospective studies and heterogeneity of key variables. There remains, despite research paucity, the need to encourage early cannabis cessation and higher-quality research to inform clinical practice.

1. Introduction

While the efficacy of antipsychotic medication in the treatment of psychotic disorders is well documented (Leucht et al., 2009, 2012, 2013, 2017; Samara et al., 2016; Tiihonen et al., 2017; Zhang et al., 2013), there is still unexplained variation in outcome with meta-analytic data suggesting that 37.9% of patients will achieve long-term symptomatic remission (Lally et al., 2017). In general, response rates to antipsychotic medications are reported in the range of 40%−90% (Remington et al., 2013; Zhu et al., 2017) with large proportions of patients showing little or complete non-response from illness onset (Ajnakina et al., 2017). For those patients who respond well initially the risk of relapse is very high in the years following onset (Alvarez-Jimenez et al., 2009; Gleeson and Gleeson, 2005; Tiihonen et al., 2017; Zipursky et al., 2014). Owing to the deleterious effects of relapse, which impairs functional recovery among patients (Alvarez-Jimenez, 2012a; Clausen et al., 2014; van der Meer and Velthorst, 2015), impacts upon the health of care-givers (Kingston et al., 2016; Sin et al., 2016) and constitutes a considerable cost for healthcare systems compared to maintenance therapies (Lafeuille et al., 2013; Nicholl et al., 2010), the identification of amenable risk factors has the potential to improve patient outcomes by informing interventions and the development health policy. Emerging evidence suggests that cannabis use is associated with increased relapse outcomes (Colizzi et al., 2018; Schoeler et al., 2016a, 2016b, 2016c) which might be due to an effect on antipsychotic treatment failure (Patel et al., 2016; Pelayo-Teran et al., 2014) and/or medication adherence (Foglia et al., 2017; Garcia et al., 2016; Schoeler et al., 2017a). Discriminating between the reasons leading to antipsychotic treatment failure, including medication non-adherence as one cause, is challenging and suggests that findings of increased relapse outcomes among cannabis users may be the result of determinants that are not mutually exclusive. Compared to antipsychotic treatment failure the effect of cannabis use on medication adherence is largely well-established with meta-analytic data from 11 studies demonstrating increased odds of non-adherence among users compared to non-users (OR = 2.46, 95% CI [1.97, 3.07], $p < .001$; Foglia et al., 2017). Due to the paucity of existing literature the association between cannabis use and antipsychotic failure, which has direct implications for patient outcomes, remains conjectural and requires clarification. To extend previous research on the topic this

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systematic review sought to summarise evidence from naturalistic randomised-controlled, observational and case-control studies regarding the effect of cannabis use on antipsychotic treatment failure among patients with psychosis.

2. Methods

2.1. Protocol

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Liberati et al., 2009). The methods used for data acquisition are detailed below in accordance with a previous meta-analysis by Foglia et al. (2017). The Cochrane Library was searched for reviews and protocols with similar objectives around the time of writing and none were identified.

2.2. Eligibility criteria

2.2.1. Types of studies

Naturalistic randomised-controlled, observational (prospective, retrospective, cross-sectional) or case-control studies presenting data on the quantitative effects of cannabis use on antipsychotic treatment failure among users and non-users with psychosis.

2.2.2. Population

Individuals, of any age, diagnosed with a psychotic disorder per standardised criteria (DSM-IV: American Psychiatric Association, 1994 or ICD-10: World Health Organization, 1992) were considered. A minimum of two groups were required for study inclusion: the first documenting evidence of cannabis use assessed by self-report, urine toxicology screening or per standardised diagnostic criteria (abuse or dependence) and the second a comparative non-use, or possibly former-use, group.

2.2.3. Outcome measures

The main outcome of interest, antipsychotic treatment failure, was broadly defined for the purposes of this review as a lack of treatment effectiveness which may manifest as: poorer treatment response (e.g., higher rates of non-response or partial response according to symptom reduction scores), decreased symptomatic remission, an increased prescription of unique antipsychotic medications, increased rates of treatment resistance indexed by recognised criteria (Andreasen et al., 2005) or proxy evidence (e.g., Clozapine prescription) and increased antipsychotic dosages during treatment or at discharge. A heterogeneous definition of treatment failure was utilised given the limited evidence base to capture all relevant available literature.

2.2.4. Additional criteria

Studies were required to be published in a peer reviewed journal and available as a full-text article written in English. Articles not available in full-text were excluded to reduce the likelihood of bias through selective reporting in abstracts. In the case of polysubstance-use studies were included if cannabis was the most frequently used substance, analyses were conducted separately for each substance or other substances were controlled for. If the presence of psychotic symptoms was unclear or samples were highly heterogeneous studies were included only when most participants were prescribed antipsychotic medication. Articles derived from the same cohort (e.g., overlapping cohorts) were excluded with data drawn from the article which most closely fulfilled the eligibility criteria. If necessary, authors of screened articles were contacted to clarify aspects of their study design, sample and outcomes of interest.

2.3. Information sources

2.3.1. Database search

An advanced search of Ovid databases: Embase (1974–2018, week 34); Journals@Ovid Full Text (August 17, 2018); OvidMEDLINE® In-Process and Other Non-Indexed Citations (August 17, 2018); PsycINFO (1806-August Week 2, 2018) was conducted on August 8th, 2018 using the following terms: psychosis OR psychot* OR schizophren* OR bipolar* OR schizoaff* AND cannabis OR marijuana AND treatment-failure OR treatment-respon* OR non-response OR partial-response OR remission OR unique-antipsychotics OR Clozapine OR antipsychotic-dose OR discharge-antipsychotic.

2.3.2. Supplementary sources

The reference lists of full-text articles screened for inclusion were manually searched as supplementary data sources.

2.4. Data extraction and quality assessment

Articles identified from database searching were assessed using a novel assessment tool consisting of 7 rated-items (adapted from Beards et al., 2013; Appendix 2). As with previous reports, this review utilised a three-point rating system (0–2) and by accumulating scores classified articles as having weak (0–4), moderate (5–9) or strong (10–14) reporting strength. Consequently, from each study the following data was extracted: (1) study-specific: name of first-author, year and country of publication, study design, sample characteristics (e.g., process of selection/recruitment, sample size, data attrition, mean age, gender and diagnosis distributions) and duration of follow-up or audited period; (2) outcome-specific: measurement data (e.g., type and number of sources, whether subjective or objective and the frequency of assessments); (3) analysis-specific: details of the statistical methods employed to examine the quantitative effects of cannabis use with reference to relevant statistics (p values, effect sizes and confidence intervals as appropriate) and whether analyses were adjusted for confounding variables.

3. Results

3.1. Study selection

A total of 253 articles were identified from database searching, with 81 of these removed after adjustment for duplicates. Of the remaining articles, 164 were excluded during title and abstract screening for not meeting eligibility criteria. Eight articles were subject to full-text screenings and manual reference searches which identified one additional relevant article. Two articles were excluded at this stage. Seven unique articles were selected for inclusion in the final qualitative synthesis (See Fig. 1 for PRISMA flow diagram).

3.2. Study characteristics

Articles with outcomes pertaining to the effects of cannabis use on antipsychotic treatment failure among users and non-users with psychosis are summarised in Table 1. The extracted studies reported on a total sample of 9147 participants; samples per study ranged from 85 to 5531. On average 62.7% of participants were male and, based on the six studies with available data, aged 36.70 (standard deviation = 12.5). Of note one study reported on the age of participants at first presentation to psychiatric services. Most of the studies were conducted in Europe (two in the UK, one in Spain and one in Hungary), one was conducted in the United States and two more in Australia. Regarding the distribution of diagnoses, all studies included participants with schizophrenia spectrum disorder with one reporting solely on this group. Three studies reported on samples consisting of participants with bipolar disorder, none reported solely on this group, and six studies included

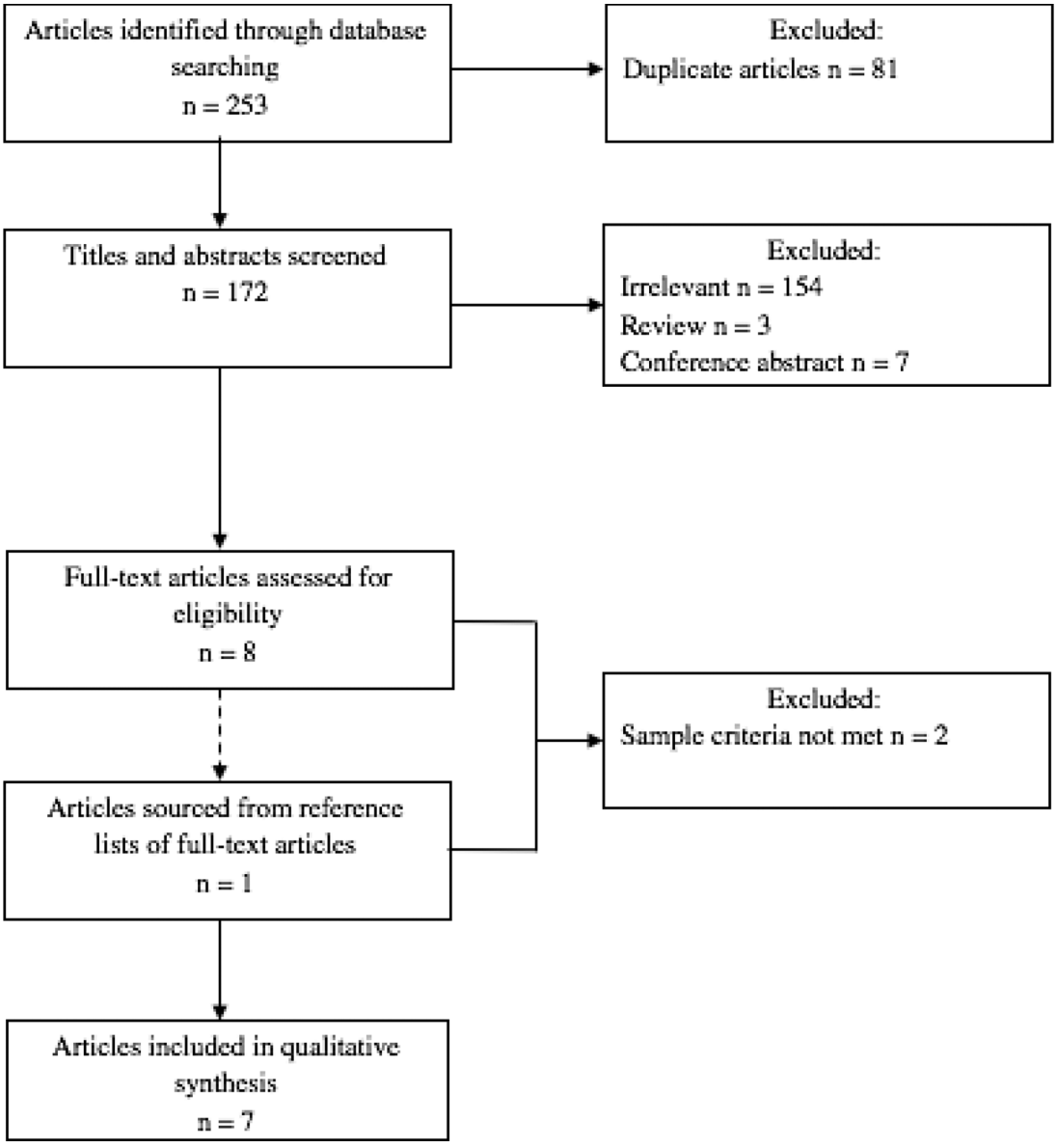

Fig. 1. PRISMA flow-diagram for antipsychotic treatment failure search.

individuals diagnosed with other psychotic disorders (including affective disorders). Regarding study design, most of the included articles were observational besides one study adopting a naturalistic randomised-controlled design. Of the observational studies: one was cross-sectional retrospective, one cross-sectional prospective, three longitudinal retrospective and one longitudinal prospective. Durations of follow-up or audited period were available for all studies and ranged from 1.38-months to 60-months (mean = 23.2-months). Five studies

Table 1
Characteristics of studies investigating cannabis' effects on antipsychotic treatment failure and medication adherence.

Database search	Study and location	Sample size[a]	Gender *n* (%)	Mean age (SD)	Diagnosis[b]	Study design
Treatment failure						
	Babatope et al. (2016), US	5531	3830 Male (69.3%)	37.55 (12.68)	1, 3	Cross-sectional retrospective
	Colizzi et al. (2016a), UK	205	130 Male (63.4%)	29.6 (9.9)[c]	1, 2 (100%), 3	Longitudinal prospective
	Makkos et al. (2011), Hungary	85	55 Male (64.7%)	27.92 (5.08)	1	Longitudinal retrospective
	Patel et al. (2016), UK	2026	1295 Male (63.9%)	n/a	1, 2 (100%), 3	Longitudinal retrospective
	Pelayo-Teran et al. (2014) Spain	161	108 Male (62.1%)	27.33 (7.76)	1, 3	Naturalistic randomised-controlled
	Schimmelmann et al. (2012), Australia	99	48 Male (48.5%)	17.1 (1)	1, 2 (100%), 3	Longitudinal retrospective
	Siskind et al. (2017), Australia	1040	705 Male (67.21%)	37.62 (10.83)	1, 3	Cross-sectional prospective

Note. Data presented as n (%) or mean (SD) unless stated otherwise.
[a] Based on the analysis between cannabis use and outcomes of interest.
[b] 1 = schizophrenia spectrum disorder; 2 = bipolar disorder (% with psychosis); 3 = other psychosis, including affective.
[c] Age at first presentation to psychiatric services.

Table 2
Quality assessment of studies investigating cannabis' effects on antipsychotic treatment failure and medication adherence.

Database search	Study	Selection bias	Sample size	Attrition	Design	Adjustment	Other substances	Quality of measurement	Total
Treatment failure									
	Babatope et al. (2016)	1	2	1	0	2	0	0	6/14
	Colizzi et al. (2016a)	1	2	0	2	1	1	0	7/14
	Makkos et al. (2011)	1	0	2	1	1	1	1	7/14
	Patel et al. (2016)	1	2	0	1	1	0	1	6/14
	Pelayo-Teran et al. (2014)	2	1	2	2	2	0	0	9/14
	Schimmelmann et al. (2012)	1	1	2	1	1	1	1	8/14
	Siskind et al. (2017)	1	2	1	1	2	1	0	8/14

Note. Data presented as quality scores obtained through use of an adapted assessment tool (Beards et al., 2013; refer to Appendix 2 for details).

had durations equal to or longer than 12-months.

3.3. Reporting strength and study quality

As shown in Table 2, studies extracted were adjudged to have moderate reporting strength with scores ranging from 6 to 9 (mean = 7.29). Generally, studies scored poorly for adjustment of other illicit substances, four studies assessed substances besides cannabis, and measurement quality because studies tended to employ single measures of cannabis use usually at first presentation to psychiatric services and proxy-measures for treatment failure taken at single-time points. Of note, studies often utilised objective measures to quantify treatment failure. Of the remaining items studies scored moderate-high when assessed for selection bias, sample size, data attrition, study design and adjustment for relevant confounders. One study used randomised methods of sampling whilst others included incident cases or control groups. Four of the seven studies reported on samples of more than 200 participants and data attrition was relatively low, although two studies rated highly based on rates of missing data due to their research designs rendering other measures non-applicable (e.g., loss to follow-up or refusal to participate). As previously mentioned, most of the included articles were observational besides one study adopting a naturalistic randomised-controlled design. Moderate-to-high scores were given for the adjustment of relevant confounders, most adjusted for basic demographics whilst three studies adjusted for confounders relating to baseline functioning or illness severity. Finally, an assessment score of 10 is indicative of methodologically robust research (Beards et al., 2013) and therefore constitutes as good-quality evidence on which to evaluate the effects of cannabis use on antipsychotic treatment failure. No study scored this highly. Overall study quality was heterogeneous and with a clear lack of well-designed longitudinal prospective studies.

3.4. Qualitative data synthesis

Seven articles (Table 3) met search criteria and reported on the effect of cannabis use on antipsychotic treatment failure among users ($n = 2454$) and non-users ($n = 6706$) with psychosis. Babatope et al. (2016) reported that cannabis users were discharged with significantly lower geometric mean chlorpromazine equivalent doses of antipsychotics compared to non-users (431.22 ± 2.20 vs. 485.18 ± 2.21, $p < .001$), however this effect was no longer significant after adjusting for age, gender, ethnicity and length of hospitalisation (0.99, 95% CI [0.92, 1.10]). Investigating the effect of cannabis use on symptomatic remission, Colizzi et al. (2016a) reported increased odds of non-remission at 1-year follow-up for cannabis users compared to non-users (multiple: OR = 2.60, 95% CI [1.09, 6.23], $p = .03$ adjusted for age, gender, ethnicity, relationship status, employment status and level of education). Makkos et al. (2011) reported no significant differences between participants, per urine toxicology status, for mean chlorpromazine equivalent dosages of antipsychotic medication for acute therapy, although Olanzapine was prescribed to patients with a negative toxicology status in significantly higher doses for long-term therapy (19.29 ± 1.89 vs. 13.61 ± 6.96 mg/day, $p = .04$). In a longitudinal retrospective study of first-episode psychosis patients, Patel et al. (2016) demonstrated that cannabis use at first presentation to psychiatric services increased the prescription of unique antipsychotic medications (multiple: Incident Rate Ratio (IRR) = 1.13, 95% CI [1.02, 1.25], $p = .02$) at 5-year follow-up. Cannabis use also increased the risk of Clozapine prescription (cumulatively) at 5-year follow-up (multiple: OR = 1.14, 95% CI [0.77, 1.71], $p = .51$). Unadjusted mediation analyses revealed that treatment failure, as indexed by the prescription of unique antipsychotic medications, partially mediated the effect of cannabis use on the frequency of admission (proportion mediated = 21.3%, $\beta_{\text{indirect effect}} = 1.09$, 95% CI [1.01, 1.18], $p = .003$), length of admission (51.4%, $\beta_{\text{indirect effect}} = 17.9$, 95% CI [2.4, 33.4], $p = .002$) and likelihood of compulsory admission (42.3%, $\beta_{\text{indirect effect}} = 1.27$, 95% CI [1.03, 1.58], $p = .003$). The greatest effect of mediation was for days spent hospitalised. Another study, (Pelayo-Teran et al., 2014), adopted a naturalistic randomised-controlled design and examined the effect of cannabis on the short-term response to antipsychotic medication, based on symptom score reductions, reporting that cannabis use was associated with trajectories of poorer outcome. Comparing responders to other treatment trajectories, cannabis use was associated with increased odds of non-response (OR = 15.9, $p = .001$), slow partial response (OR = 7.3, $p < .001$) and partial response (OR = 4.4, $p = .006$) for positive psychotic symptoms and lower odds of dramatic treatment response (OR = 0.35, $p = .003$) for disorganised psychotic symptoms. Consistent with Colizzi et al. (2016a), Schimmelmann et al. (2012) reported that persistent cannabis use when compared to non-use predicted lower rates of symptomatic remission (OR = 0.11, 95% CI [0.03, 0.44], $p = .002$ adjusted for premorbid functioning). Examining substance-use across the life-time and within the past-year among those prescribed Clozapine, the licensed pharmacological agent for patients with a resistant illness, compared to other antipsychotics Siskind et al. (2017) reported similar rates of life-time (multiple: OR = 1.05, 95% CI [0.76, 1.43], $p > .05$ adjusted for chronicity and diagnosis) but lower past-year rates of cannabis use among patients prescribed Clozapine (multiple: OR = 0.39, 95% CI [0.28, 0.56], $p < .001$ adjusted for chronicity and diagnosis.

4. Discussion

This is the first systematic review to summarise evidence regarding the effect of cannabis use on antipsychotic treatment failure, in accordance with a previous meta-analysis, among users and non-users with psychosis. In line with study objectives, seven articles were extracted from database searching and selected for qualitative synthesis. Findings extend previous research by suggesting that cannabis use has measurable deleterious effects on the course of psychotic disorders, through antipsychotic treatment failure, which are determined by patterns of cannabis continuation. Study quality was heterogeneous and no study was adjudged as methodologically robust according to quality assessment scores.

Findings that the adverse effects of cannabis use on antipsychotic treatment failure are determined by patterns of continuation are

Table 3
Summary findings of studies investigating cannabis' effects on antipsychotic treatment failure and medication adherence.

Database search	Study	Cannabis use	Outcomes of interest	Findings
Treatment failure				
	Babatope et al. (2016)	UTS: positive 660 (11.9%) vs. negative 4871 (88.1%)	Geometric mean chlorpromazine equivalent doses	Linear regression: Effect of cannabis use on chlorpromazine equivalent doses was no longer significant after adjusting for age, gender, ethnicity and length of hospitalisation confounded the effect of lower chlorpromazine equivalent doses (0.99, 95% CI [0.92–1.10]).
	Colizzi et al. (2016a)	CEQ-M: use at baseline: 134 (65.4%); use at follow-up: 136 (66.3%)	Remission (absence of psychotic symptoms for 30-days according to PPHS at follow-up): yes 93 (45.4%) vs. no 112 (54.6%)	Logistic regression: Cannabis use increased the odds of non-remission at 1-year follow-up (multiple: OR = 2.60, 95% CI [1.09, 6.23], p = .03 adjusted for age, gender, ethnicity, relationship status, employment status and level of education)
	Makkos et al. (2011)	UTS: positive 42 (49.4%) vs. negative 43 (50.6%)	Mean chlorpromazine equivalent doses	ANOVA: No differences between groups comparing mean chlorpromazine equivalent dosages for acute therapy. Olanzapine was administered to UTS negative patients in significantly higher doses for long-term therapy (19.29 ± 1.89 vs. 3.61 ± 6.96 mg/day, p = .040, n = 17).
	Patel et al. (2016)	Cannabis use within 1-month of admission: 939 (46.3%)	Unique number of antipsychotics prescribed; Clozapine prescription; relapse outcomes (length in days and number of admissions plus likelihood of compulsory admission)	Negative binominal regression: Cannabis use associated with an increased prescription of unique antipsychotic medications (multiple: IRR = 1.13, 95% CI [1.02, 1.25], p = .02) and increased frequency of admission (multiple: IRR = 1.50, 95% CI [1.25, 1.80], p < .001) at 5-year follow-up. Logistic regression: Cannabis use associated cumulatively with an increased likelihood of Clozapine prescription (multiple: OR = 1.14, 95% CI [0.77, 1.71], p = .51) and increased likelihood of compulsory admission (multiple: OR = 1.55, 95% CI [1.16, 2.08], p=.003) at 5-year follow-up. Linear regression: Cannabis use associated with a greater number of days admitted (multiple: β = 35.1 days, 95% CI [12.1, 58.1], p = .003) at 5-year follow-up. Multiple regression analyses adjusted for age, gender, ethnicity, marital status and psychotic diagnosis. Mediation analysis: Number of unique antipsychotics prescribed mediated the increased frequency of hospital admission (proportion mediated = 21.3%, $_{\text{indirect effect}}$ = 1.09, 95% CI [1.01, 1.18], p = .003), increased likelihood of compulsory admission (42.3%, $_{\text{indirect effect}}$ = 1.27, 95% CI [1.03, 1.58], p = .003) and greater number of days spent in hospital (51.4%, $_{\text{indirect effect}}$ = 17.9, 95% CI [2.4, 33.4], p = .002).
	Pelayo-Teran et al. (2014)	Self-reported: cannabis use 82 (47.13%) vs non-use 92 (52.87%)[a]	Short-term response to antipsychotic medication according to symptom reduction (SANS-SAPS)	Mixed regression models: Comparing responders to other treatment trajectories, cannabis use associated with poorer treatment response. Increased odds of non-response (OR = 15.9, p = .001), slow partial response (OR = 7.3, p < .001) and partial response (OR = 4.4, p = .006) for positive symptom dimension and lower odds (OR = 0.35, p = .003) of dramatic response for disorganised symptom dimension.
	Schimmelmann et al. (2012)	Life time cannabis use: 65 (65.7%); cannabis use at baseline: 53 (53.5%); course of cannabis use: non-use 44 (44.4%), decreased-use (29.3%) and persistent-use (26.3%)	Symptomatic remission (absence of positive symptoms for at least 12-weeks according to PANSS and CGI-S)	Logistic regression: Compared to non-use persistent cannabis use, adjusted for premorbid functioning, predicted lower rates of symptomatic remission (OR = 0.11, 95% CI [0.03, 0.44], p = .002) whilst decreased-use was not predictive.

(*continued on next page*)

Table 3 (*continued*)

Database search	Study	Cannabis use	Outcomes of interest	Findings
	Siskind et al. (2017)	Lifetime cannabis use: 544 (69.2%) Clozapine-negative vs. 180 (70.6%) Clozapine-positive; past-year-use: 298 (37.8%) Clozapine-negative vs. 50 (19.7%) Clozapine-positive	Rates of substance-use among patients prescribed Clozapine	Logistic regression: Similar rates of life-time cannabis use (multiple: OR = 1.05, 95% CI [0.76, 1.43], $p > .05$ adjusted for chronicity and diagnosis), but lower past-year rates of cannabis use among patients prescribed Clozapine (multiple: OR = 0.398, 95% CI [0.282, 0.563], $p < .001$ adjusted for chronicity and diagnosis).

Note. Data presented as *n* (%) or mean (SD) unless stated otherwise. CGI-S = clinical global impressions-severity, PANSS = positive and negative syndrome scale, SANS = scale for the assessment of negative symptoms, SAPS = scale for the assessment of positive symptoms, UTS = urine toxicology screening.

[a] Based-on data from Pelayo-Teran et al. (2008).

concordant with previous studies examining medication adherence (Colizzi et al., 2016a; Foglia et al., 2017; Schimmelman et al., 2012; Schoeler et al., 2017a, 2017b) and relapse outcomes (Schoeler et al., 2016a,2016b, 2016c,2017a) providing further evidence that cannabis use is a robust risk factor for poor outcome in psychosis. It remains unclear how other determinants, such as cannabis-potency, affect outcomes related to antipsychotic failure though adverse effects have already been reported for relapse outcomes (Schoeler et al., 2016c) and medication adherence (Schoeler et al., 2017b).

Extracted studies generally found effects in favour of cannabis use having measurable deleterious effects on prognostic outcomes, yet some studies deviated. One possible explanation, which findings from this review and wider literature support, for no reported differences among users and non-users for chlorpromazine equivalent doses in two studies (Babatope et al., 2016; Makkos et al., 2011) is that neither assessed cannabis use parameters which are relevant determinants of cannabis' adverse effects. Findings of lower past-year rates of cannabis use among psychosis patients prescribed Clozapine, despite similar lifetime rates of use, compared to other antipsychotics (Siskind et al., 2017) may be the result of selection bias whereby cannabis users are less likely to be considered for a Clozapine trial because of associations with non-adherence. Treatment resistance, which necessitates the prescription of Clozapine according to clinical guidelines, is defined as an inadequate response to sequential trials of two different antipsychotics at adequate dose, duration and adherence. Concordant with selection bias and findings from Howes et al. (2012a) that prescribing practices often deviate from clinical guidelines because patients are prescribed other antipsychotics instead of Clozapine, polypharmacy and/or dosages exceeding recommendations upon failing two sequential trials of medication, Patel et al. (2016) reported that cannabis users were prescribed 2.68 ± 3.98 unique antipsychotics at 5-year follow-up. Alternatively, Clozapine may be more effective than other antipsychotics at reducing cannabis consumption in a population with a high prevalence of use (Wilson and Bhattacharyya, 2016).

There are several potential mechanisms through which cannabis use may contribute to antipsychotic treatment failure and medication non-adherence in psychosis. Poor antipsychotic treatment response is associated with cannabis use (Colizzi et al., 2016a; Patel et al., 2016; Pelayo-Teran et al., 2014; Schimmelman et al., 2012) and has been linked to a non-dopaminergic pathophysiology as found in those with a treatment resistant illness (Demjaha et al., 2014; Egerton, 2016). Antipsychotic treatment exerts its effect by acting as a dopamine antagonist in line with findings of elevated presynaptic dopamine function in psychosis (Howes et al., 2012b). Findings that regular cannabis use may downregulate the dopaminergic system (Bloomfield et al., 2014; Sami et al., 2015) and instead produce glutamatergic abnormalities (Colizzi et al., 2016b) suggests that users with psychosis may be comparable to treatment-resistant patients as elevated glutamate levels are associated with a poor response to antipsychotic medication (Egerton, 2016). This is consistent with evidence that a single dose of δ-9-tetrahydrocannabinol, the main psychoactive component in cannabis, increases levels of striatal glutamate in controls (Colizzi et al., 2018b) and findings of reduced dopamine synthesis capacity among cannabis users who meet criteria for dependence (Bloomfield et al., 2014) because of reported differences amongst treatment responders and non-responders (Jauhar et al., 2018). Articles investigating medication adherence consistently suggest an adverse effect of cannabis use which might be due to cannabis' effect on symptomatology and/or memory function. Several follow-up studies suggest that continued cannabis use is associated with a significant worsening in the ratings of psychotic (Clausen et al., 2014; Seddon et al., 2015; Schoeler et al., 2016a; van der Meer and Velthorst, 2015) and depressive symptoms (Gonzalez-Ortega et al., 2015; Gonzalez-Pinto et al., 2009). Comparisons of symptomatic and functional outcomes between non-users, former users and continued users differ significantly suggesting that abstinence from cannabis and other substances may improve prognostic outcomes

(Clausen et al., 2014; Gonzalez-Pinto et al., 2009; Mullin et al., 2012; Schoeler et al., 2016a,2016b,2016c; Weibell et al., 2017). Furthermore, studies examining the effects of δ-9-tetrahydrocannabinol challenge in controls (Bhattacharyya et al., 2009, 2012, 2015) and psychosis patients using antipsychotics (D'Souza et al., 2005) demonstrate exacerbations in psychotic symptoms and cognitive impairments in both groups. Non-remitting symptoms will inevitably affect the perceived efficacy of antipsychotic medication concordant with negative attitudes towards medication being an often-cited reason for non-adherence (Velligan et al., 2017). Prolonged cannabis use is additionally associated with neuroanatomical changes in several major areas associated with memory function (Batalla et al., 2013; Lorenzetti et al., 2016; Rigucci et al., 2016; Rocchetti et al., 2013). Interestingly, effects such as those on prospective memory may interfere with an individual's ability to regularly adhere to prescribed medications. Analyses restricted to patients with a non-relapsing illness course revealed that continued use of high potency cannabis remained a significant predictor of non-adherence (Schoeler et al., 2017b) suggesting that factors other than those on symptomatology may also contribute to non-adherence.

Discrimination between the reasons for antipsychotic treatment failure is challenging because determinants, such as medication adherence, may not be mutually exclusive. These variables likely share a large amount of variance and, as demonstrated by Colizzi et al. (2016a), could reside on a common causal pathway between cannabis use and symptom non-remission. Furthermore, the relationship between medication non-adherence and antipsychotic treatment failure may be bidirectional whereby antipsychotic treatment may fail due to non-adherence, despite treatment having the desired effects, or patients are non-adherent due to the lack of treatment efficacy. To address bidirectional causal effects future studies could examine alternative mediation models with treatment failure and medication adherence as mediating variables in the association between cannabis use and prognostic outcomes. Given the supposed shared variance the two mediating variables should be linked in a causal chain and not modelled to resist the effects of one another (Hayes, 2013) to better quantify potential bidirectional effects. It is important to consider the use of appropriate control groups in the design of future studies examining the effects of continued cannabis use on prognostic outcomes among patients with psychosis. While non-users have typically been utilised as controls for this purpose, such groups differ significantly across multiple domains confounding the interpretation of results. In contrast, because continued users and former users share a common vulnerability towards initiating cannabis, including former users as a comparator group addresses any potential confounding effects from differential vulnerabilities to poor outcomes associated with the initiation of cannabis use and examines whether patterns of cannabis use contribute to antipsychotic treatment failure independently. Including former users, as opposed to or, in addition to non-users, as control groups might also help to reduce the potential for bias by addressing pre-existing group differences because evidence suggests that cannabis users and non-users with psychosis have distinct clinical, prognostic and neurocognitive trajectories (Sami and Bhattacharyya, 2018).

4.1. Limitations

Whilst observational studies can provide valuable information when double-blind randomised-controlled trials are not feasible these research designs are more prone to potential bias and less methodologically rigorous. Overall, there was considerable heterogeneity across the included studies with none constituting as methodologically robust according to assessment scores. Some of this heterogeneity might be inherent to the problem under examination at the study-outcome level and here at the review-level. As such, several limitations need addressing.

Firstly, whilst efforts were made to produce a comprehensive literature search by using a broad definition of antipsychotic treatment failure such inevitably reduces study specificity leading, potentially, to the inclusion of irrelevant data. Nevertheless, using relevant terminology in conjunction with thorough methods of data extraction as not to hamper the interpretation of the included studies through poor or incomplete reporting and recommendations from PRISMA guidelines (Liberati et al., 2009) this review provides useful insight which could inform higher-quality studies. Future studies, to further clarify the association between cannabis use and antipsychotic treatment failure, should aim to examine a range of proxy measures suitable for longitudinal prospective designs such as the number of unique antipsychotics prescribed, rates of (non)-remission and various relapse outcomes commenting particularly on associations with cannabis use parameters.

Secondly, the distribution of diagnoses varied among the extracted studies meaning that results should be interpreted cautiously when inferring effects of cannabis within specific clinical populations. For instance, careful consideration should be given regarding cannabis' effects on affective disorders as study findings could be due to undisclosed effects on pharmacological agents besides antipsychotics, such as mood stabilisers and antidepressants, which were prescribed adjunctively in the included studies. Indeed, three studies have reported reduced rates of symptomatic remission at 6-month (Bereza, 2016) and 24-month follow-up (Kim et al., 2015; Zorrilla et al., 2015) among continued cannabis users, compared to non-users, diagnosed with bipolar disorder and schizoaffective disorder. Despite this issue, recent findings provide a transdiagnostic role of dopamine dysfunction amongst individuals with affective disorders whom experience psychotic symptoms (Jauhar et al., 2017) concordant with findings of elevated presynaptic dopamine function in psychosis (Howes et al., 2012b). As such, the differential response to antipsychotic medications and supposed non-dopaminergic pathophysiology among cannabis users is likely to be consistent regardless of diagnosis due to the same underlying dysfunction. Even amongst heterogeneous samples, findings from this review suggest that cannabis use contributions to antipsychotic treatment failure.

Thirdly, the quality and methods by which studies measured cannabis use varied, creating a source of heterogeneity and potential bias. Six studies assessed cannabis use with single measures, two objectively through urine toxicology screenings at admission to psychiatric services and one (Makkos et al., 2011) adopted a combination. Of note, two studies employing longitudinal prospective and retrospective designs assessed cannabis use at multiple time-points. Despite this inherent issue prevalence rates of cannabis use, at baseline, were well represented in this review (45.6%, $n = 6$) and are comparable with previous meta-analytic estimates (33.7%, 95% CI [0.29, 0.38], $n = 35$; Myles et al., 2016) albeit higher. A growing body of literature suggests that cannabis use parameters such as patterns of continuation and potency are relevant determinants of adverse outcome at follow-up (Colizzi et al., 2016a; Schimmelman et al., 2012; Schoeler et al., 2016a, 2016b, 2016c, 2017a, 2017b). It's therefore concerning that such have been infrequently investigated in the available literature, underscoring a need for the routine detailed assessment of cannabis use parameters in future studies and in clinical practice to clarify which aspects of cannabis exposure (e.g., age of initiation, history, potency and patterns of continuation) are relevant moderators of its effects.

Insofar as high-quality research is necessary to evaluate the effects of cannabis use to inform clinical practice and improve prognostic outcomes for patients, the considerable heterogeneity and moderate reporting strength of the included studies prevents definitive conclusions from being made and thus warrant improved methodologies in future studies.

4.2. Clinical implications

Notwithstanding the above limitations, the results of this review have implications for the treatment of psychosis patients with co-

morbid cannabis use by suggesting possible targets for intervention. For instance, interventions aimed at optimising treatment response may mitigate the effects of cannabis use and improve clinical outcomes. A growing body of literature suggests that treatment non-response at 2-weeks can be highly predictive of subsequent symptomatic improvement (Samara et al., 2015). As such, implementing alternative treatment strategies early-on may improve prognostic outcomes for cannabis users with psychosis. Emerging evidence suggests that Clozapine is effective at reducing cannabis use and craving among patients with psychosis (Machielsen et al., 2017; Siskind et al., 2017; Tang et al., 2017; Wilson and Bhattacharyya, 2016) and achieves a more pronounced response as a second-line treatment compared to switching antipsychotics which may provide rationale for early-use with the aim of preventing periods of enduring symptoms and disability (Agid et al., 2011, 2013; Okhuijsen-Pfeifer et al., 2018). The potentially superior efficacy of Clozapine treatment in patients with co-morbid cannabis use may offer insight into the suspected parallels between this group and treatment-resistant patients and should warrant more prospective investigations among larger samples (Colizzi et al., 2016b). Comparisons of non-adherence rates between non-users and former users of cannabis do not different significantly, suggesting that abstinence from cannabis use may improve medication adherence (Foglia et al., 2017). If so, this could account for the improvements demonstrated among patients in several studies after substance discontinuation (Clausen et al., 2014; Mullin et al., 2012; van der Meer and Velthorst, 2015; Weibell et al., 2017). As treatment discontinuation increases the odds of psychotic relapse up to 4-fold (Alvarez-Jimenez et al., 2012b; De Hert et al., 2015) the implementation of strategies to optimise adherence is important and has the potential to improve patient outcomes. For example, improving the tolerability of antipsychotic medications has implications for rates of compliance as treatment-induced effects are often cited as reasons for treatment discontinuation (Velligan et al., 2017). Alternatively, long-acting injections are associated with reduce all-cause treatment failure rates compared to oral antipsychotic medications besides Clozapine (Tiihonen et al., 2017). Future studies should investigate strategies to improve medication adherence among psychosis patients with co-morbid cannabis use for possible benefits to prognostic outcomes.

Furthermore, this review underscores the importance of implementing strategies to address cannabis use parameters. For instance, future interventions could encourage complete cessation or at least periods of sustained abstinence, if complete cessation is unlikely, because evidence suggests that intermittent use is not associated with increased relapse outcomes (Schoeler et al., 2016c), medication non-adherence (Schoeler et al., 2017b) or non-remission (Schimmelman et al., 2012). Likewise, encouraging the use of less potent cannabis strains may improve relapse rates (Schoeler et al., 2016c) and medication adherence (Schoeler et al., 2017b). Encouraging intermittent-use may also appease those unwilling to remain completely abstinent due to increased drug-dependence (Freeman and Winstock, 2015) or lacking insight into the adverse effects of regular cannabis use (Katz et al., 2010; Schimmelman et al., 2012). Clinical trials have shown that combinations of cognitive-behavioural therapy, motivational enhancement therapy, motivational interviewing and contingency management are moderately effective in reducing cannabis use, but are limited in achieving sustained abstinence, among dependent-users without psychiatric disorders (Sherman and McRae-Clark, 2016; Walther et al., 2016). Furthermore, pharmacological treatments show little efficacy either independently or adjunctively to psychological treatment in this population. Unfortunately, the moderate effects of psychological interventions are not duplicated among cannabis users in psychiatric populations (Cooper et al., 2015). There is a clear need for newly developed interventions and research into which strategies may reduce cannabis use in those with psychosis. This review provides insight into future directions, although confirmation of suspected gains in prospective randomised-controlled comparative trials is required before further implementation.

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Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112523.

Appendix 1. Database search strategy

Treatment failure:

(1) ((psychosis or psychot* or schizophren* or bipolar* or schizoaff*) and (cannabis or marijuana) and (treatment-failure or treatment-respon* or non-response or partial-response or remission or unique-antipsychotics or Clozapine OR antipsychotic-dose OR discharge-antipsychotic)). ab, ti.
(2) remove duplicates from 1

Appendix 2. Quality assessment tool

(1) Selection Bias

Score
0 Non-random selection process, or sampling method not reported
1 In case-control/cohort studies sample consists of either incident-cases, or randomly sampled controls, or no controls
2 In case-control/cohort studies, sample consists of incident-cases and randomly sampled controls, or random selection process in general population studies

(1) Sample size (on-which analysis for relevant outcomes were performed)

Score
0 < 100
1 100–200
2 > 200

(1) Attrition (what proportion (%) of the sample refused to participate, were lost at follow-up or had large amounts of missing data resulting in their exclusion from statistical analysis?)

Score
0 > 50% data loss
1 50% − 20% data loss
2 < 20% data loss

(1) Design

Score
0 Cross-sectional retrospective
1 Cross-sectional prospective, or longitudinal retrospective
2 Longitudinal prospective

(1) Adjustment

Score
0 No adjustment for confounders
1 Adjustment for basic demographics, or no difference among groups existed
2 Potential relevant confounders, such as those related to baseline functioning or illness-severity, were adjusted for in addition to basic demographics, or no differences among groups existed

(1) Other substances

Score
0 No consideration of other substances, independent effects of cannabis not distinguished from other substances or unaccounted effects of other substances
1 Other substances were assessed but not controlled for
2 Other substances assessed and adjusted for

(1) Quality of Measurement (e.g., cannabis use and treatment failure)
(a) Source of measurement

Score
0 Not specified or single-measure
1 Two different measures
2 > two different measures, or two types (including an objective measure)

(a) Frequency of measurement

Score
0 Not specified, or single time-point
1 Measured at multiple time-points (2–5), but no > once per year
2 Measured at multiple time-points (2–5) more often than once per year, or 5+ measurements

Scores obtained by averaging the above scores (per variable, then as a sum of these scores) and rounding to the nearest whole-number.

Example:

Study A. Cannabis (2/2 + 0/2)/2 = 1; Treatment failure (2/2 + 1/2)/2 = 1.5; (1 + 1.5)/2 = 1.25 (Rounded = 1)

(1) Total

Score (minimum 0; maximum 14)

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