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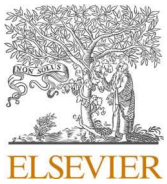

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Review

Cannabis induced psychosis: A systematic review on the role of genetic polymorphisms

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ABSTRACT

Objective: Cannabis sativa is a recreational drug commonly consumed in Europe and is getting popularity for both recreational and therapeutic use. In some individuals, the use of cannabis leads to psychotic disorders. This systematic review summarizes the current evidence linking genetic polymorphisms and inter-individual susceptibility to psychosis induced by cannabis.

Method: Studies published from 2005 to 2020 were identified through Medline using PubMed, Web of Science and Scopus database and searches were conducted according to PRISMA guidelines. Initial search was performed with terms: "cannabis induced psychosis" AND "genetics".

Results: From the initial group of 108 papers, 18 studies met our inclusion criteria. Many of the findings revealed associations with genetic polymorphisms modulations of genes involved directly (COMT, DRD2 and DAT) or indirectly (AKT1) to dopamine pathways. The most consistent finding was with COMT rs4680, where the presence of the Val allele was associated with a higher risk for cannabis-induced psychosis. This higher susceptibility was also reported for AKT1 (rs2494732) with the CC genotype. Of note, the only genome-wide association study identified a significant signal close to the cholinergic receptor muscarinic 3 represented by rs115455482 and rs74722579 predisposing to cannabis-induced hallucinations and remarkably no dopaminergic target was found.

Conclusion: Actual evidence supports the role of dopamine in cannabis induced psychosis. However, most of genetic polymorphism studies have as a starting point the pre-existing dopaminergic theoretical basis for psychosis. This alerts to the importance of more broad genetic studies. Integrate genetic results into biological systems may enhance our knowledge of cannabis induced psychosis and could help in the prevention and treatment of these patients.

1. Introdution

Cannabis sativa is a recreational drug commonly consumed in Europe, especially during late adolescence and early adulthood. This is the source of a pool of molecules known as plant cannabinoids or phytocannabinoids. There are at least 70 cannabinoids found in the cannabis plant [1] but research has been focused mainly on (−)-trans-Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

According to the European Monitoring Centre (EMCDDA) in 2021, 15.4% of 15–34 years old European individuals reported to have used cannabis at least once during the last year [2]. Besides the leisure use, 'medical cannabis' is nowadays being considered as a possible treatment to different disorders and clinical symptoms (epilepsy [3], multiple sclerosis [4], chronic pain [5], depression [6], anxiety [7], nausea and/or vomiting [8], etc). Although the use of medicinal cannabis has already increased, facts from basic and medical research committed to this topic are still scarce, with insufficient quality data proving cannabis clinical efficacy. Furthermore, the functional consequences of its use remain largely unknown. In addition, consistent findings associated cannabis use with the development of schizophrenia or other psychoses [9].

Experimental and epidemiological data demonstrated that frequent

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cannabis users have a higher risk of developing transitory psychotic symptoms that include suspiciousness, paranoia and hallucinations [10]. Investigation studies consistently reported an association between psychotic disorder and cannabis use, with a two-fold increased risk for psychotic disorder associated with the use of significant quantities of cannabis [11–13].

The biological mechanism underlining the association between cannabis use and psychotic syndromes are yet to be fully identified.

It is currently know that cannabis or its components exert their biological effects through several receptors that take part of the Endocannabinoid System (eCB) [14]. This system is a disseminated network of receptors, signalling molecules, and metabolic/ catabolic enzymes and its main functions comprise preserving the homeostasis of central nervous system, cognition and memory mechanisms and controlling of motor function and signs of analgesia. Research in the late 60 s led to the discovery that the psychotropic effects of cannabis are produced mainly by THC. Years later, it was described that many of the THC effects are mediated through the Cannabinoid receptor type 1 CB1[15] located in the brain and one of the components of the Endocannabinoid System.

CB1 receptor modulates neurotransmitter, as glutamate and GABA, release, preventing the development of excessive neuronal activity in the central nervous system. This will impact other pathways as the dopaminergic system, implicated in psychosis. CB1-induced GABA release will initiate a complex inhibitory signalling cascade culminating in the excitation of dopaminergic neurons. It is known that acute or chronic THC exposure produces complex and possibly durable adaptive changes in dopaminergic system/dopamine signalling pathways with deficits in dopaminergic-related functions [16]. Interaction at different levels of the dopaminergic and eCB systems are claimed to be associated with the development of several psychopathologic disorders such as psychosis or schizophrenia.

There is also sufficient data sustaining that a spectrum of cognitive deficits observed in schizophrenia can be prompted in healthy individuals by acute THC administration, as is the case of aberrant salience [17]. Anomalous salience processing and attribution are the basis of a large amount of the psychotic symptoms observed in schizophrenia [18] therefore, its study is of particular interest to those who investigate the effects of cannabis on psychosis.

However, it is also needed to consider that the dysregulation in dopamine release and availability in these disorders may also be influenced by impairments in receptors or enzymes of the dopaminergic pathway.

Nevertheless, cannabis affects individuals in different ways and the basis of this unpredictable sensitivity is uncertain. In 1971, D.J. Spencer and colleagues described the situation like the “drug acts as a precipitating factor in predisposed individuals who for some reason have ill-understood personality traits which render them susceptible to this type of psychotic reaction.”[19]. It is also known that some users will only have transitory psychotic syndromes, with different degrees of severity, whilst others will have lifetime neurological damage. How this inter-individual variability in the susceptibility to the cannabis’ effects can be explained? Why do only a few of these cannabis-users will develop long term mental problems? Why can only a few recovers? Clearly, these questions should be answer before widespread of medicinal cannabis. Can there be influence of unidentified susceptibility genetic or epigenetic factors? In the last decade, some reviews addressing this issue have been published [20–22] however they are mainly traditional literature reviews with the inclusion of confounding syndromes. In the present study we present another point of view performing a systematic review, where i fixed methodological process are used. This allows to minimise bias and ensure future replicability. So, strictness, transparency, and replicability can be achieved [23]. Although there are several genetic association studies analysing polymorphisms in dopaminergic genes and schizophrenia [24–29] we choose not to include it in this metanalysis. Our aim is to analyse possible genetic contributors in the development of cannabis-induced psychosis. We think that the inclusion of schizophrenia patients, can convey misleading conclusions regarding the effect of cannabis, evaluating individuals predisposed to psychotic symptoms regardless of cannabis use. In line with that, another exclusion criterion imposed was the absence of a general non-clinical population. In addition to these exclusion criteria, no other restrictions were imposed, either concerning the clinical outcome, nor the genetic analysis performed, nor the study design. Finally, a new quality assessment was used, to achieve a global view about the real value of the included publications.

Thus, assuming the current importance in the knowledge of the biologic effects of cannabis use in the development of psychotic syndromes, in the present review, we aim to summarize the current evidence on the impact of genetic polymorphisms in the inter-individual variability and susceptibility to the effects of cannabis.

2. Materials and methods

2.1. Search strategy and study selection

This study was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [30] for a literature review of published data accessing the role of genetic polymorphisms on cannabis induced psychosis. Published studies were rescued after a literature search including three electronic databases: PubMed [https://www.ncbi.nlm.nih.gov/pubmed/], Web of Science [http://www.isiwebofknowledge.com] and Scopus [www.ssopus.com]. The literature search was carried out on published data in English, accessing the role of genetic polymorphisms on cannabis induced psychosis until April 2022 (date of last search 01/04/2022), using the following terms: “cannabis induced psychosis” AND “genetics” and “psychosis + genetic polymorphisms + cannabis”.

The studies identified using the electronic databases were independently screened by two authors. Conflicts were discussed between the two authors to reach an agreement.

2.2. Eligibility and inclusion/exclusion criteria

Studies were considered for inclusion after analysis of the full text and confirmation of one of the next criteria: (a) articles concerning the influence of cannabis in the trigger of psychotic symptoms; and (b) articles relating cannabis use associated with an elevated risk of schizophrenia. The following information was collected from the selected studies: authors’ name; publication year; analysed polymorphism; and obtain results. The reference list of eligible articles was later supervised for further articles.

In order of the restricted information in this field, all manuscripts that demonstrated to be relevant to the topic were included in this review. Only marginal exclusion criteria were used and no constraints on the design of the study were used. We excluded: a) any study whose title and abstract clearly indicated that it declined to meet the earlier described search terms; b) reviews, letters, book chapters, editorials, and case reports; c) articles where full text was not available; d) articles that did not evaluate the influence of cannabis use; e) articles that only included in the study schizophrenia patients.

2.3. Quality assessment

To establish the methodological value of the included studies, we examined the quality of the research problem together with the quality of the data disclosed. Qualitative analysis using checklists, or scores assess for basic science studies, are rare. Nevertheless, in spite of experimental conditions are more controlled in basic science leading to the least probability risk of bias, the need for a rigorous and quantitative evaluation of what has already been published is real. In this study, the qualitative analysis was performed independently by the two authors according to a quality checklist with 14 criteria developed specifically

for basic science studies by Cosme D. et al. [31] (Table 1). Each criterion of the checklist was scored as follows: information not available in the published paper (0 points); limited information provided (1 point); complete information regarding that aspect (2 points). For each study, the scores of all criteria were added and divided by the maximum score (28 points) to obtain paper's overall quality score.

In the next section, in line with the main aim of the review and the extracted data, results will be synthesized and presented by gene studied.

3. Results

The initial data base search yielded 238 citations. Based on an initial screening of the titles and abstracts 220 articles were excluded because did not address any of the outcomes of interest or were reviews of the existing literature, and 23 were selected for full text examination. Bibliographies of pertinent papers were screened, and further 6 additional studies were considered qualified. Twenty publications met our eligibility criteria and were included in our review.

A PRISMA flow diagram (Fig. 1) demonstrates the procedure followed to select the papers used in this review. Table 2 summarizes relevant data found in the included articles.

Looking at Table 2, the first thing that stands out is the large number of studies that investigate the influence of the Catechol-O-methyltransferase (COMT) gene/enzyme in this process. Out of the 18 included articles, twelve analyse polymorphisms in COMT gene and eight of that described positive associations with pertinent features of psychosis and cannabis use. The other gene with a significant number of studies in this context is AKT1. Seven articles describe the research done on the possible role of this gene in the association between cannabis use and the trigger of psychosis disorder. Some of these articles are very forceful works, with large population samples and emerging even confirmation studies of previous results, despite some limitations in the communication of the results. It will be important to highlight that the vast majority of these studies focus on genes involved in dopaminergic pathways.

Another fact of relevance in Table 2, is the study design of the included publications. These studies can be essentially divided in two main groups, observational and interventional research. The first group contain most of the included articles and we can find case/control studies, also known as "retrospective studies", cohort studies, a type of longitudinal study that follows research participants over a period of time [32]. The remaining studies, can be encompassed in the group of interventional research, being mostly placebo-controlled studies in which volunteers are randomly assigned to either a test group receiving the experimental intervention or a control group receiving a placebo.

Considering de quality assessment done for all the articles included in this review, we can report that all of the studies have an evaluation superior to 50%, and the vast majority (n = 14) are located in the upper quartile. It is interesting to note that the two criteria with lower scores are the definition of the endpoints to study, allocated to the second group "Purpose and hypothesis", and evaluation by independent observers; blinding; evidence of independent repetitions in the data collection.

Currently, there are already some studies describing associations between genetic variations in components of endocannabinoid and dopaminergic systems and the cannabis effects on mental disorders. Studies focused on variations in COMT enzyme or AKT1 genes are some examples.

3.1. Catechol-O-methyltransferase (COMT)

COMT metabolizes catechol neurotransmitters dopamine, noradrenaline and adrenaline that are involved in several physiological features like mood, cognition and stress response [33]. This enzyme plays an essential role in the breakdown of dopamine (DA) in the Prefrontal Cortex [34] contrasting to the striatum where DA is cleared by a transporter.

The gene encoding the COMT enzyme, located at chromosome 22q11 (OMIM 116790, gene ID 1312), has functional polymorphisms that contribute to the interindividual variability in COMT activity in humans. COMT Val158Met polymorphism (rs4680), which causes a valine to methionine amino acid substitution, was described for the first time in 2005 as a possible modifier factor of the development of psychiatric disorders in cannabis consumers. Caspi and colleagues[35] described that carriers of the COMT Valine158 allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they were adolescent-onset cannabis users.

Some years later Henquet et al. [36] tried to corroborate these findings with a double blind, placebo-controlled crossover study in a European population. They have report carriers of the Val allele as most sensitive to the use of cannabis with D-9-THC-induced psychotic

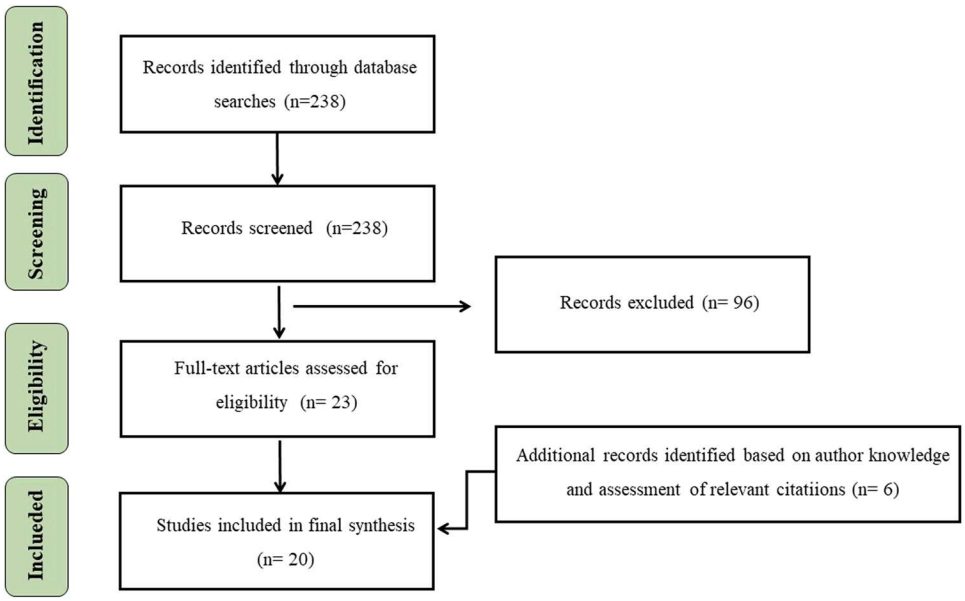

Fig. 1. PRISMA flow diagram.

Table 1
Quality assessment of the included genetic studies; scored as 0 points (information not available in the paper); 1 point (limited information provided); 2 points (complete information regarding that aspect).

REPORTING ASSESSMENT		Caspi	Henquet C.	Henquet C.	van Winkel R.	van Winkel R.	Estrada G.	Zammit	Marta Di Forti	Bhattacharyya S.	Alemany S.	Vinkers	Collizi	Tunbridge	Morgan	Lodhi R. J.	Lodhi R. J.	Cheng Z.	Bioque	Boks M. P.	Hindocha C.
Criteria		2005	2006	2009	2011	2011	2011	2011	2012	2012	2013	2013	2015	2015	2016	2017	2019	2020	2019	2020	2020
Problem definition	**1.** Scientific background and explanation of rationale	2	2	1	2	2	2	1	1	1	2	2	2	2	2	2	1	1	1	2	2
Purpose and hypothesis	**2.** Definition of the specific objectives or hypotheses	2	2	2	0	2	2	2	1	2	2	2	2	2	2	2	2	1	2	2	2
	3. Definition of the endpoints to study	1	0	0	0	1	1	2	0	o	0	1	0	1	2	0	0	2	0	1	0
Study design	**4.** Accurate description of the laboratory methodologies (easy to understand and described in enough detail to allow replication), definition of the test compounds, experimental conditions and other important information; use of validated methods	2	1	1	1	1	2	2	2	1	2	2	1	2	2	2	2	2	2	2	2
	5. Ethical review permissions, when applicable	2	2	1	0	0	2	0	2	0	2	2	2	2	2	2	0	2	2	2	2
	6. Description of the statistical methods, when adequate	2	2	2	2	2	2	2	2	0	2	2	2	2	2	2	2	1	2	2	2
Data collection	**7.** Obtain valid data and ensure that it is reliable	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	8. Evaluation by independent observers; blinding; evidence of	1	1	0	0	0	0	0	0	0	2	1	0	2	0	1	0	0	0	0	0

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Table 1 (*continued*)

REPORTING ASSESSMENT		Caspi	Henquet C.	Henquet C.	van Winkel R.	van Winkel R.	Estrada G.	Zammit	Marta Di Forti	Bhattacharyya S.	Alemany S.	Vinkers	Collizi	Tunbridge	Morgan	Lodhi R. J.	Lodhi R. J.	Cheng Z.	Bioque	Boks M. P.	Hindocha C.
Criteria		2005	2006	2009	2011	2011	2011	2011	2012	2012	2013	2013	2015	2015	2016	2017	2019	2020	2019	2020	2020
	independent repetitions																				
Analysing data and manuscript drafting	**9.** Cite relevant scientific papers when presenting evidence	**1**	2	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	2	2
	10. Accessible and transparent presentation of data throughout the paper (including the appropriate measures of precision/ variance)	1	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2	2	2	2	2
	11. Critical discussion of the results; comparison with relevant research on the field	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	12. Draw consistent conclusions based on the evidence presented in the paper	2	1	1	2	2	2	2	2	2	2	2	2	2	2	2	1	2	1	1	2
	13. State the contribution to cumulative scientific knowledge and the practical implications of the findings	2	2	2	1	2	2	1	2	2	2	2	2	2	2	2	2	1	0	2	2
	14. Disclose conflicts of interest and declaring funding sources	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	0	2
Criteria overall score		**1.71**	**1.64**	**1.36**	**1.29**	**1.57**	**1.79**	**1.57**	**1.50**	**1.29**	**1.86**	**1.86**	**1.64**	**1.93**	**1.86**	**1.79**	**1.43**	**1.57**	**1.36**	**1.57**	**1.71**
Standard deviation		**0.45**	**0.61**	**0.72**	**0.88**	**0.73**	**0.56**	**0.73**	**0.73**	**0.84**	**0.52**	**0.35**	**0.72**	**0.26**	**0.52**	**0.56**	**0.82**	**0.62**	**0.81**	**0.73**	**0.70**
Maximum score		**85.7%**	**82.1%**	**67.9%**	**64.3%**	**78.6%**	**89.3%**	**78.6%**	**75.0%**	**64.3%**	**92.9%**	**92.9%**	**82.1%**	**96.4%**	**92.9%**	**89.3%**	**71.4%**	**78.6%**	**67.9%**	**78.6%**	**85.7%**

Table 2
Studies on genetics in the context of cannabis induced psychosis.

Study	Population	Study design	Target Sample	Gene/SNP/ Mutation	Results/Conclusions	Association
Caspi et al. 2005	New Zealand's South Island	Longitudinal, prospective	803 individuals	COMT (rs4680)	Carriers of the COMT Val allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis.	Yes
Henquet C. et al. 2006	Netherlands	Double-blind, placebo-controlled cross-over design	Psychotic disorde r(n = 30); healthy controls (n = 32)	COMT (rs4680)	Carriers of the Val allele were most sensitive to D-9-THC-induced psychotic experiences, but this was conditional on prior evidence of psychometric psychosis liability.	Yes
Henquet C. et al. 2009	Europe (Neederlands, Spain, UK)	Case/Control	Psychotic disorder (n = 31) and healthy controls (n = 25)	COMT (rs4680)	Val allele cannabis users with psychometric evidence of psychosis liability have increased levels of hallucinations.	Yes
van Winkel R. et al. 2011	Netherlands and Flanders, Belgium	Family-based analysis	801 patients with psychosis and 740 unaffected siblings	179 SNPs in 46 genes	Using different epidemiological designs, evidence was found that rs2494732 SNP in AKT1 may also moderate possible long-term developmental effects of cannabis on psychotic disorder.	Yes
van Winkel R. et al. 2011	Netherlands and Belgium	Case/Control	1120 patients with non-affective psychotic disorder, 1057 siblings of these 1120 patients, 919 parents and 590 unrelated controls	AKT1 (rs2494732)	AKT1 (rs2494732) individuals with C/C genotypes have an approximately 2-fold odds of being diagnosed with a psychotic disorder when having used cannabis.	Yes
Estrada G. et al. 2011	Spain	Case/Control	Psychiatric inpatients (n = 157). 80 with schizophrenia-spectrum and 77 with non-psychotic disorders	COMT (rs4680)	val/val genotype carriers showing an earlier age at psychotic disorders onset with cannabis use.	Yes
Zammit et al. 2011	UK	Longitudinal	2630 individuals	COMT (6 different SNPs)	Cannabis increases risk of psychosis irrespective of underlying COMT genotypes.	No
Marta Di Forti et al. 2012	UK	Case/Control	First episode psychosis (n = 489); control (n = 278)	AKT1 (rs2494732)	Carriers of the AKT1 (rs2494732) C/C genotype with a history of cannabis use showed a greater than twofold increased likelihood of a psychotic disorder	Yes
Bhattacharyya S. et al. 2012	UK	Placebo-controlled	35 healthy volunteers	DAT1 (3'UTR VNTR) and AKT1 (rs1130233)	Individuals with G/G genotype to AKT1 rs1130233 and also carriers of the 9-repeat allele of the DAT1 3'UTR VNTR, had increased sensitivity to the psychotic effects of d-9-THC.	Yes
Alemany S. et al. 2013	Spain	/	533 individuals from the general population	COMT (rs4680)	Val carriers exposed to childhood abuse are vulnerable to the psychosis-inducing effects of cannabis.	Yes
Vinkers et al. 2013	Netherlands	Cross-sectional study	918 from CannabisQuest and 339 from general population	COMT (rs4680)	Childhood maltreatment result in an increase of psychotic experiences in Val/ Val individuals who use cannabis.	Yes
Collizi et al. 2015	UK	Case/Control	First episode of psychosis (n = 272); controls (n = 234)	DRD2 (rs1076560)	Among cannabis users, carriers of the DRD2 (rs1076560) T allele showed a 3-fold increased probability to suffer a psychotic disorder.	Yes
Tunbridge E. M. et al. 2015	UK	Placebo-controlled	82 participants	COMT (rs4680)	COMT genotype alters the cognitive, but not the psychotic effects of acutely administered THC in healthy volunteers.	No
Morgan C.J.A. et al. 2016	UK	/	422 cannabis users	COMT (rs4680) and AKT1 (rs2494732)	AKT1 (rs2494732) C allele predict acute psychotic response to cannabis.	Yes
Lodhi R. J. et al. 2017	Canada	/	169 psychotic disorders	COMT (rs4680)	Cannabis users with Val/Val genotype develop psychosis earliest in life.	Yes
Lodhi R. J. et al. 2019	Canada	/	167 psychotic disorders	BDNF (rs6265) and AKT1 (rs2494732)	No significant effects between genotypes and cannabis effect.	No
Cheng Z. et al. 2019	USA	GWAS	7206 Individuals (European Americans + African Americans)	GWAS + meta-analysis	Reported one GWS association signal, represented by rs115455482 and rs74722579 at the CHRM3 locus, with cannabis-induced hallucinations.	Yes
Bioque et al. 2019	Spain	Case/Control	321 patients with first episode of psychosis (FEP) and 241 healthy controls	15 SNPs in three candidate gene regions	FAAH rs2295633 SNP genetic polymorphism was associated with a greater risk of presenting a FEP in subjects with relevant cannabis use	Yes
Boks M. P. et al. 2020	Netherlands	GWEIS	1262 individuals	GWEIS	rs7958311 from P2RX7 gene was associated with risk for a high level of psychotic experiences in regular cannabis users and in those with high levels of lifetime cannabis use	Yes
	UK	Case/Control				No

(*continued on next page*)

Table 2 (*continued*)

Study	Population	Study design	Target Sample	Gene/SNP/ Mutation	Results/Conclusions	Association
Hindocha C. et al. 2020			First episode psychosis patients (n = 143); controls (n = 92); young adult (YA) cannabis users n = 485	AKT1 (rs2494732), COMT (rs4680) and FAAH (rs324420)	Variation in AKT1, COMT or FAAH was not associated with cannabis-induced psychotic-like experiences (cPLEs)/ euphoric experiences (cEEs).	

experiences, however, only in individuals with conditional on prior evidence of psychometric psychosis liability. The same research team affirmed these observations in a case/control study were described that carriers of the Val allele with prior evidence of psychometric psychosis liability showed an increase in hallucinations after acute cannabis exposure in daily life [37]. More recently, Tunbridge et al. performed the largest study up to now to investigate the impact of COMT genotype on reply to experimentally administered THC, and the first using a non-clinical cohort. The results show that COMT genotype alters the cognitive, but not the psychotic effects of acutely administered THC in healthy volunteers [38].

Another group of studies found associations related with the age of onset. In these cases, they argued that brain maturation in the cannabis-exposure moment can be important. Estrada et al. in 2011[39] through a study with a sample of 157 young Caucasian psychiatric inpatients concluded that COMT Val158Met genotype seems to modulate the association between cannabis and psychotic disorders especially in individuals who were exposed to cannabis at an early age. This work refers that the combined effect of the COMT Val allele and the age of cannabis-consumption onset should be considered when studying the origin of psychotic symptoms and their prevention. In the same line, Lodhi et al. [40] corroborate these findings, demonstrating that those who used cannabis before the age of 20 years, having the Val/Val genotype could be associated with the earliest age of diagnosis of psychosis.

Other research groups have investigated the interdependent outcomes of COMT polymorphisms and additional environmental factors. An analysis of 533 individuals from the general Spain population found a significant three-way interaction among childhood abuse, cannabis use and the COMT gene in positive psychotic experiences. Summarizing, exposure to childhood abuse and cannabis use increased psychotic experiences scores in COMT Val allele carriers [41]. Confirming these findings, Vinkers et al. found in a cross-sectional study that high levels of childhood maltreatment result in a marked increase in psychotic experiences in Val/Val individuals who use cannabis [42].

Regarding this interaction between cannabis and COMT rs4680 polymorphism, some studies did not find any association. In 2011, two studies analysing the role of COMT polymorphisms reported negative results [43,44]. Recently, an analysis in a UK population conducted by Morgan et al. lack to establish a direct involvement of the functional COMT rs4680 polymorphism in mediating acute psychotic response to cannabis [45]. These results have been recently confirmed by Hindocha et al., using a subsample of the Genetic and Psychosis (GAP) study [46]. In a case control study, they reported that COMT did not modulate specific psychotomimetic response to cannabis [47].

The collection of articles related to COMT presented above gene are the group with better maximum score in the quality assessment. There are three publications with more than 90% and the article from Tunbridge E. M. et al. 2015 [38] achieved the best score of all included, with a value of 96%.

3.2. AKT1

AKT1 is a serine/threonine-protein kinase that regulates many processes including metabolism, proliferation, cell survival, growth, and angiogenesis. Signalling involving AKT1 kinase appears to be essential for the normal development and function of the nervous system. Studies have suggested a role for AKT1 kinase in cell-to-cell communication among nerve cells (neurons). In the brain, *AKT1* plays a role in modulating synaptic plasticity and is involved in intracellular trafficking of dopamine and norepinephrine[48].

The serine-threonine protein kinase AKT1 gene, located at 14q32.32, has been already associated with schizophrenia susceptibility[49]. Levels of protein kinase AKT1 were 68% lower in individuals with schizophrenia than in controls, and are thought to play a role in the modulation of the association between cannabis and psychotic disorders. The involvement of the AKT1 kinase in these pathologies is thought happen through DA receptor signalling with AKT1 regulating dopaminergic striatal signalling both as it relates to DRD2 availability and DA release [50].

The first study to address this association was performed in 2011 with a population from Netherlands and Belgium with a family-based analysis that comprised 801 patients with psychosis and 740 unaffected siblings. In this initial approach, van Winkel et al. analyse 179 SNPs in 46 genes and demonstrated that cannabis users with the AKT1 rs2494732CC genotype had a twofold increased risk of being identify with a psychotic disorder [43]. AKT1 rs2494732 and cannabis interaction was supported in the case-only ($p = 0.007$), case-sibling ($p = 0.04$) and case-control ($P = 0.057$) analyses. These results were confirmed later in the same year in a study focused only in AKT1 gene [51]. Given these results, it can be concluded that AKT1 may have a role on psychosis expression associated with cannabis use, probably through a mechanism of cannabinoid-regulated AKT1/GSK-3 signalling. Recently, Di Forti et al. report an even more robust association between rs2494732 and cannabis use – associated psychosis [52]. Based on *an apriori* hypothesis, they genotyped only the rs2494732 in a sample of 489 first episode of psychosis and 278 healthy controls and found that the effect of lifetime cannabis use on risk of psychosis was significantly influenced by the rs2494732 ($p = 0.014$). Carriers of the rs2494732 CC genotype with a history of cannabis use revealed a twofold increased risk possibility of developing a psychotic disorder ($OR = 2.18$) when compared with users who were rs2494732 TT. In the same year, Bhattacharyya S. and colleagues [53] had already demonstrated the importance of AKT1 gene in the cannabis - induction psychotic symptoms. Using a placebo-controlled, within-subject design in 35 healthy volunteers they concluded that an increase in psychotic symptoms was higher in individuals who were rs1130233 GG. The authors also reported that this effect could be influenced by other genes and δ-9-THC has been demonstrated to markedly attenuate the striatal activation in rs1130233GG GG carrier individuals [53].

In the year of 2016 Morgan et al. published new information about the role of AKT1 in this context. With a study including 422 cannabis users, they provide the first evidence that the acute effect of cannabis can be predicted by the polymorphism rs2494732 of the AKT1 gene. They reported that AKT1 rs2494732 C allele was associated with increased psychotomimetic symptoms after smoking cannabis [45].

Despite all previous results with positive associations, Lodhi et al. in a population from Canada [54] and Hindocha et al. with a case/control study in UK, investigated the role of AKT1 (rs2494732) on age of onset of psychosis and cannabis-induced psychotic-like experiences/euphoric experiences. In these both studies, it was concluded that AKT1 did not influence any of the mentioned features.

Very recently, genetic (AKT1 rs1130233) and epigenetic modulation was found to influence the psychotomimetic and neurofunctional effects

of THC in healthy humans [55].

These publications on serine-threonine protein kinase AKT1 gene, don't have a quality score as high as the COMT group. Only one of the articles [45] achieved a score above 90%.

3.3. Other genes

Although the majority of the published studies focus on COMT and AKT1 genes, since 2012 some research has been made in the association of other genes with cannabis use-induced psychosis.

DAT1 gene, encoding for dopamine transporter, mediates the active re-uptake of DA from the synapse, has a VNTR (variable number tandem repeat) polymorphism in the 3′ UTR, consisting of a sequence of 40 nucleotides repeated three to eleven times. This polymorphism has been shown to affect DAT1 expression, with the 10-repeat allele being associated with lower DAT levels than the 9-repeat allele [56]. The possible influence of this variation in the induction of psychotic symptoms in healthy volunteers who had minimal previous cannabis use was investigated by S. Bhattacharyya et al. in a placebo-controlled study [53]. The authors examined the acute effects of δ-9-THC on psychotic symptoms in 35 healthy volunteers and suggest that individuals carrying the risk variant, 9-repeat allele, of the DAT1 3′UTR VNTR have an increased sensitivity to the psychotic effects of δ-9-THC.

Following the same line of thought (the importance of dopamine in this process) in 2015, M. Colizzi et al. tried to struggle the lack of research on the role of DRD2 gene in the context of the association between cannabis use and psychosis and/or psychosis-related phenotypes [57]. They genotyped a case-control study of 272 patients with their first episode of psychosis, 234 controls, and a sample of 252 healthy subjects, for a functional variation in *DRD2* rs1076560. After the analysis, they described that among cannabis users, carriers of the DRD2, rs1076560T allele showed a 3-fold increased probability to suffer a psychotic disorder. In its conclusion they refer that variation of the DRD2 gene may modulate the psychosis-inducing effect of cannabis use.

Brain-derived neurotrophic factor (BDNF) gene is another marker already studied in the context of cannabis exposure and psychosis. BDNF plays an important role in the development of the central nervous system having impact on the serotonergic signalling, glial cells [58], hippocampus neurons and the brain cortex [59]. Many researchers believe that genetic variation in the BDNF gene could be involved in the aetiology and pathogenesis of psychiatric disorders. In this context the most studied gene variation is the rs6265 (196 G>A) polymorphism that changes protein sequence Val66Met. In 2019, J. Lodhi et al. published a study where they investigated the main effects of BDNF rs6265 on age of onset of psychosis (AoP), adjusted for gender and age at regular cannabis use [54]. The group have genotyped 167 patients with psychosis and cannabis use information were collected using a self-reported electronic questionnaire and they described using Kaplan-Meier analyses that gender ($p = 0.010$) and age at regular cannabis use ($p = 0.0029$) significantly affected AoP, while rs6265 ($p = 0.39$) did not.

A large study, published in 2019, reported the results of the first genome-wide association (GWAS) of cannabis-induced hallucinations (Ca-HL) carried-out in a population of European-Americans (4291) and African Americans (3624). They identified a genome-wide significant signal close to the cholinergic receptor muscarinic 3 (CHRM3) represented by rs115455482 and rs74722579, predisposing to Ca-HL in European Americans, with the finding nominally replicated in African Americans. Previous investigations using animal models [60] support the concept that the CHRM3 gene play an inhibitory role in dopamine release, and the blockage of cholinergic receptors, mainly muscarinic receptors, causes psychosis in normal human individuals and intensify symptoms in schizophrenic patients [61]. In the same line of this study but including environment-interaction (GWEIS), Boks et al. analysed, in a sample of 1262 individuals without a psychiatric disorder, the interactions between regular cannabis use and genotype with psychotic-like experiences (PLE) as outcome [62]. In this assessment, again, a single gene was identified. A putative role for the purinergic P2X7 receptor in the biological mechanisms underlying the relationship between cannabis and psychosis was suggested. In addition to important functional results, a SNP in the P2RX7 gene (rs7958311) was associated with risk for a high level of psychotic experiences in regular cannabis users ($p = 1.10 \times 10–7$) and in those with high levels of lifetime cannabis use ($p = 4.5 \times 10–6$).

Another gene included in the studies of the relation between cannabis use and psychosis was the FAAH gene. It has been recently observed in a clinical trial that cannabidiol (CBD) a potential FAAH inhibitor, increased plasma levels of anandamide in schizophrenia diagnosed patients [24]. This effect was correlated with clinical improvement. The first publication that analysed this possibility was a case/control study conducted in Spain, where 15 selected SNPs related to the endocannabinoid system and cannabis were evaluated in a cohort of 321 patients with a first episode of psychosis (FEP) and 241 matched healthy controls. The most striking conclusion achieved was that the probability of presenting a FEP was tenfold higher (OR: 10.69) in cannabis users who were homozygote carriers of the rs2295633 T allele [63]. Within this context, the most recent study included in this review [47] analysed again a possible role of this gene on the link between cannabis and psychosis. FAAH rs324420 polymorphism has been analysed in a cohort of 143 FEP patients, 92controls and 485 young adult cannabis users. This non-synonymous polymorphism leads to changes in protein structure, with a 30% reduction in the performance of the enzyme reported for the rs324420A allele carriers. The study by Hindocha et al. did not observe any association between his genetic variant and cannabis-induced psychotic-like experiences or euphoric experiences.

This last set of publications is the one with worst score in the quality assessment. This can be justified by the fact that most studies in this group did do not mention some important aspects from study design and methods.

4. Discussion

Cannabis is one of the most popular consumed drugs, especially among young people but its use is also considered a risk factor for trigger or worsening mental disease. Due to this idea there has been severe discussion in numerous countries over whether cannabis should or not be legalized. Although the increased use of medicinal cannabis, in several disorders, namely epilepsy [3], multiple sclerosis [4] or chronic pain [5], related epidemiological studies have shed light on the probable psychotomimetic effects of cannabis and demonstrated the need for stricter regulations on cannabis use. These observations have led to a new question: does cannabis use primarily induce psychosis in those who are at increased risk? Can cannabis induce psychotic symptoms in individuals who otherwise would not develop psychosis? The role of genetics in this process could help in the answer to those questions, and we aimed here to summarize the current evidence on the impact of genetic polymorphisms in the inter-individual variability and susceptibility to the effects of cannabis. What it is known is that most cannabis users do not develop psychosis; others develop light psychotic symptoms, existing yet other groups with more serious situations with acute psychotic disorders or even when cannabis plays a trigger to schizophrenia. This observed inter-individual variability in the susceptibility to the effects of cannabis could certainly be related with genetic (and/or epigenetic?) factors.

With this review we were able to reveal that most of available studies and consistent results are undoubtedly related with changes in dopaminergic pathways. It should be kept in mind, however, that these results are also due to the fact that this kind of research has the starting point pre-existing theoretical sources. In other words, the current hypothesis for the biological elucidation of schizophrenia is founded on alterations in dopaminergic system so these genetic studies will focus on genes related to these pathways. On this basis, it is important to

reinforce the significance of more inclusive genetic studies (GWAS) in order to conduct future research and open new doors for studies in other possible biological pathways. Beyond GWAS, in the last decade, new approaches with the same importance are being developed trying to overcome the difficulty in understanding and see the complete picture of a complex disease like psychosis. One of these examples is the use of polygenic risk scores (PRSs), a subcategory of Polygenic Score(s) (PGS), that evaluates the risk to develop a disease or trait, calculating the weighted sum of the several common allele variants obtained in GWAS [64].

Another example of these new methods are the ones that point the interplay between predisposing genes and environmental exposure. In the last years, an increasing consideration has switched to the weight of this risk factor. Genome-wide environment interaction studies (GWEIS) and exposome studies are two possible methodologies. The complex role of environment factors in the development of mental disorders has been addressed with the exposome approach. In fact, cannabis use is included in the cumulative environmental exposure score for schizophrenia (exposome score for schizophrenia) [65].

In this review, with the intention to minimizing the bias we did not include studies comprising patients with schizophrenia. In fact, in the field of schizophrenia there are several genetic association studies analysing polymorphisms in genes with a role in dopaminergic system [25–29]. However, these studies may give misleading conclusions regarding the effect of cannabis, as they evaluate individuals already predisposed to psychotic symptoms regardless of cannabis use.

Initial investigations on involvement of genetic factors in cannabis induced psychosis date from 2005 [35]. From then on, other studies were available. Although not much information is yet published, COMT and AKT1 are the two most studied genes, but the reported results are controversial. The inconsistency in results and the reduced number of studies prompt the need for more research.

Many studies with different results analysed the association between Catechol-O-Methyltransferase gene rs4680 and the cannabis consumption and the majority reported positive association with Val allele. The rs4680 Val allele is described as leading to an increase of prefrontal dopamine catabolism and thus lower extracellular dopamine levels [66]. This polymorphism is associated not only with cannabis use-induced psychotic experiences [36,37], but also with earlier onset of these experiences [39,40], more responsive to THC induced psychosis [36] or in a correlation with childhood abuse [41,42].

Regarding AKT1 gene the consistence of the results published, go in the same line. One of the studies [53] analysed the polymorphism AKT1 rs1130233 and reported an increase in psychotic symptoms of individuals who were G homozygotes and that this result is reinforced in combination with other genes. However, this is the only published study on the effect of AKT1 rs1130233 in cannabis induced psychosis, whereas the bulk investigates AKT1 rs2494732. For this last SNP there are three positive associations, the first one described individuals with C/C genotypes having an approximately 2-fold odds of being diagnosed with a psychotic disorder when having used cannabis [43] and the second one by the same group and using the same sample assessed cognitive performance and the results indicate that the cumulative risk-increasing effects of AKT1 rs2494732C/C genotype and cannabis use on psychotic disorder go together with selective alterations in sustained attention [51]. The last study with a positive association described that carriers of the AKT1 rs2494732C/C genotype with a history of cannabis use showed a greater than twofold increased likelihood of a psychotic disorder [52]. The remaining literature found no significant interaction between of AKT1 rs2494732 genotype and cannabis users on development of psychotic disorders.

For the other genes pointed in this review we can find positive (DAT1 3′ UTR VNTR, *DRD2* rs1076560 and CHRM3 rs115455482/rs74722579) and negative (BDNF rs6265 and FAAH rs324420) associations, but we must never forget in this case that we are looking at single studies.

A general analysis of included studies in this review demonstrated that there are several points that stand out for possible explanations on the lack of success in replicating the results.

Starting with the sample characterization, we have a great heterogeneity in the definition of phenotypes and endophenotypes, from patients with a clinical diagnosis of psychotic disorder, patients with their first episode of psychosis to healthy volunteers. The measures outcomes are also very different. We have Community Assessment of Psychic Experiences (CAPE), Positive and negative symptoms scale (PANSS), Diagnostic and Statistical Manual of Mental Disorders (DSM–5) or Phychosis Screening Questionnaire (PSQ). Another clear problem is the sample size of same studies. Consequently, researchers should go beyond replication studies and get advantage of converging results in different studies as well as an integration of results from diverse experimental approaches like epigenetics or genomic technology. One can think in the act of cannabis consumption as an environmental modifying factor, and within this context epigenetic effects must be considered. The key role of epigenetic mechanisms in different biological processes and human diseases has been clearly demonstrated over the last few years. Epigenetic changes in this context could be the result of long-term exposure to cannabis or a pre-existing condition involved in cannabis user's neurobiological vulnerability. This field is emerging in relation with psychotic disorders and accrued evidence proposes that epigenetic regulation of the genome may be responsible for gene–environment interactions at the molecular level [67–69].

We recognize our review's limitations. Firstly, there are still few studies published in the literature, we were capable to find only 18 published papers. Furthermore, the variety of measuring instruments and experimental design used in each of the published paper are different making difficult to pull together in a suitable systematic review all the collected results. However, the study was planned according to PRISMA guidelines [30], the published results are trustworthy and will certainty help in the decision on the right course for the next steps.

In conclusion, despite all the published data so far, the truth is that much is still unknown about how genetics influences cannabis-induced psychosis and the balance of these biological systems. Substantial work remains to be done before the widespread use of medical cannabis. Although the first pilot studies of pharmacogenetic-guided cannabis usage [70] the sustained research in these fields may allow a better and more rational use of cannabis, with the selection of the most appropriate therapy based on patients' genetic/epigenetic background. This tailored medicine will indeed allow improvement of therapeutic achievement, raising the cost/benefit correlation and diminishing the use of ineffective treatments with their subsequent side effects.

Identified genetic polymorphisms associated with a higher risk to develop psychosis are mostly related directly (COMT, DRD2 and DAT) or indirectly (AKT1) to the dopaminergic system. This sustains the hypothesis that an aberrant salience dopamine driven is contributing to the psychotic effect of cannabis. However, not all results are congruent and new genome wide association studies could help to identify different targets outside dopaminergic system.

Contributors

CC performed the literature search, data extraction, and writing. CC and MVC contributed equally to the study design, and to subsequent review and revision of the manuscript. All authors contributed to and approved the final manuscript.

Declaration of Competing Interest

We declare no competing interests.

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