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CONTENTS

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Schatzberg AF, Samson JA, Bloomingdale KL, et al. T*oward a biochemical classification of depressive disorders, X: urinary catecholamines, their metabolites, and D-type scores in subgroups of depressive disorders*. Arch Gen Psychiatry 1989;46:260-8.

Books:

Kaplan HI, Sadock BJ. *Comprehensive textbook of Psychiatry.* Baltimore: Williams & Wilkins 1985.

Chapters from books or material from conference proceedings:

Cloninger CR. *Establishment of diagnostic validity in psychiatric illness: Robins and Guze's method revisited.* In: Robins LN, Barret JE, editors. The validity of psychiatric diagnosis. New York: Raven Press 1989, pp. 74-85.

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CHANCE, RISK OR CAUSATION? AN OVERVIEW OF THE REVIEWS ADDRESSING THE COMPLEX RELATION BETWEEN CANNABIS AND PSYCHOSIS

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Abstract

Objectives: The debate on the association between cannabis use and development of psychosis is still. It is important to establish if the association is causal and to estimate the magnitude of this effect, as cannabis might represent a potentially modifiable risk factor. This paper aims to review the secondary literature published so far on the association between cannabis use and psychosis in order to summarise their major findings.

Materials and methods: Peer-reviewed literature addressing the effect of cannabis use on the development of psychosis published between January 2000 and August 2016 was searched in the MEDLINE. The search was filtered by language (English) and type of publication (review).

Results: Most of the reviews consistently report a significant association between cannabis use and psychosis, which could be indicative of a causal relationship. People using cannabis have at least a two-fold risk of developing psychosis compared to people who do not use it. The risk is increased in people with genetic/biological vulnerability, if the exposure to cannabis starts early in adolescence and in case of heavy cannabis use (or use of high potency cannabis). The reviewed studies also indicate that cannabis by itself it is neither a sufficient nor a necessary cause of psychosis.

Conclusions: There is an ethical imperative to inform young individuals of the probable mental health risks of cannabis use, including the risk of developing psychosis. The clearest policy implication is that cannabis use should be discouraged among young people and people with high vulnerability to psychosis.

Key words: cannabis, marijuana, psychosis, schizophrenia, genetic predisposition, adolescence, policy

Introduction

Recreational cannabis use has become almost as common as tobacco use among adolescents and young adults, as a culturally acceptable lifestyle choice [1]. In parallel, national legislations and public attitudes toward the use of cannabis are becoming more favourable to cannabis in many countries. In the USA twenty-three states have currently medical marijuana laws and four of these states (Alaska, Colorado, Oregon and Washington) have also legalized marijuana for recreational use. More people are now in favour of legalization of cannabis use than in previous years [2 3] and fewer people around the world tend to see cannabis use as risky [4-6]. No wonder that recreational cannabis use has spread globally to both developed and low- and middle-income countries [7].

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The most recent World Drug report [8] estimates that 360 million people aged 15-64 years, equivalent to 7.6% of the world adult population, use cannabis each year. The corresponding estimates for 2005 were 160 million cannabis users, 4% of the world's adult population [9]. Cannabis use is steadily increasing in West and Central Africa and continues to be high in Western and Central Europe and Oceania, as well as in North America. In the USA cannabis is the most commonly used illicit substance, with 8.4% of the adult population having used cannabis in the past 12 months, and over 22 million people who report smoking on a regular basis; the percentage of users rises to 19.6% for young adults (18-25 yrs) [10]. Similarly, cannabis is the illicit drug most commonly used by all age groups in the EU countries: an estimated 19.3 million Europeans (aged 15-64), or 5.7%, used cannabis in the past 12 months, with 14.6 million of those aged 15-34 (11.7% of this age group) [11].
In parallel, over the recent years the number of people requiring treatment for cannabis use has steadily increased [8]. A substantial body of evidence is currently available showing that cannabis use is associated with a wide range of adverse health and psychosocial outcomes, including development of cannabis use disorders or cannabis dependence, increased risks of motor vehicle accidents, use of other illicit drugs, cognitive impairment, lower levels of educational attainment and psychotic symptoms [12 13].
This latter issue poses particular concerns on a public health perspective. Epidemiologic evidence has accumulated over the last thirty years suggesting that cannabis use may be an important environmental risk factor for developing schizophrenia and related psychoses. With this regard, the pioneering study of Andreasson et al. [14] based on a 15-year follow-up of Swedish military conscripts found that heavy cannabis use was associated with a 6-fold increase in risk for schizophrenia. Debate has since ensued over whether this association is causal. A number of subsequent cohort studies [15-22] replicated Andreasson's findings showing that cannabis use increases the risk of psychosis with a dose dependent relationship and that this association is independent of other clinical and personal characteristics.
However the debate on this issue is still contentious, as researchers involved in the field do not seem to have reached a general consensus [1 12 13 23]. The number of scientific papers addressing the association between cannabis use and psychosis has dramatically increased over the past thirty years, but findings are still conflicting. Such inconsistencies pose considerable problems when it comes to interpreting findings in order to inform decisions to be taken: it is important, in fact, to establish whether the association between cannabis and psychotic disorders is causal and to accurately estimate the magnitude of this effect, as cannabis use might represent a potentially modifiable risk factor for psychosis.
This paper aims to review the secondary literature published so far on the association between cannabis use and psychosis (i.e., narrative reviews, systematic reviews and meta-analyses) in order to summarise their major findings. An early overview of systematic reviews on cannabis and psychosis was published some years ago [24]. However, this paper reviewed studies published up to 2007 and only included systematic reviews. Since this publication, several other primary and secondary research studies addressing the complex issue on relationship between cannabis and psychosis have been published; this indicates the need to update knowledge accumulated on the topic over the last ten years.

Methods

Search strategy

Peer-reviewed literature addressing the effect of cannabis use on the development of psychosis published between January 2000 and August 2016 was searched in the MEDLINE database, using terms from the United States National Library of Medicine thesaurus (Medical Subject Headings, MeSH) when available, with descriptors and Boolean operators (AND/OR) clearly defined. The following MeSH terms were included: ['Substance-related disorders' OR 'cannabis' OR 'marihuana' OR 'marijuana'] AND ['psychosis' OR 'psychotic disorders' OR 'schizophrenia' OR 'psychotic'*]. The search was filtered by species (human), language (English) and type of publication (review). The reference lists of all included reviews were also searched and a citation search of those papers which cited studies included in the review was also carried out.
Titles and abstracts and then full texts were screened to identify relevant reviews for inclusion. Only reviews (both systematic and narrative) that clearly state their objective and define the inclusion criteria were included in this study.

Results

Overall, 110 reports were identified; 62 were excluded on the basis of the title and abstract because they

were not pertinent to the objective of our review, and the full text of 50 articles was retrieved for more detailed evaluation; 8 articles were excluded because they did not fulfil the inclusion criteria. Thus, 42 article (4 systematic reviews and meta-analysis; 6 systematic reviews; 3 narrative reviews and meta-analysis; 29 narrative reviews) were finally included in the present study. More specifically, 38 reviews (both systematic and narrative) addressed the effect of cannabis use in the onset of psychosis, whereas three systematic reviews explored the effect of cannabis on transition to psychosis in clinical high risk populations

Systematic reviews and meta-analyses on the effect of cannabis on the onset of psychosis

Systematic reviews exploring the role of cannabis use on the development of psychosis together with narrative reviews which performed meta-analysis are summarized in Table I.

Seven of the 10 included reviews [25-31] explored the association between cannabis exposure and the occurrence of schizophrenia (any type), schizophrenia-like disorders, psychosis not otherwise specified, or psychotic symptoms; one review [32] assessed the association between any illicit drug use and the occurrence of any psychological or social harm, but it also included studies assessing the association between cannabis use and psychosis considered as 'psychological or social harm'; one review [28] assessed the relationship between cannabis use and affective disorders (depression, suicidal ideation or attempt, anxiety); finally, one review [33] addressed the methodological strengths and limitations of the primary cohort studies which explored the link between cannabis and psychosis, and considered research findings against criteria for causal inference, whereas another article [24] was an overview of published systematic reviews on the association between cannabis use and psychosis which assessed their methodological quality and analyzed the possible reasons for the discordant results.

Seven reviews [25-31] also performed a meta-analysis providing estimates for the risk of psychosis linked to cannabis use. They were concordant in finding an association between cannabis use and the occurrence of psychotic disorders, with an increased risk of developing psychotic symptoms or psychotic disorders in subjects who use cannabis as opposed to nonusers.

Table II shows the study design and the reference of each primary study included in the seven systematic reviews/meta-analyses providing estimates for the risk of psychosis linked to cannabis use.

Overall, 20 longitudinal cohort studies [14-20 34-44] and 8 cross-sectional studies [45-52] were included in the seven reviews. Five of the reviews [25 26 28 30 32] included only longitudinal cohort studies, whereas the other three [27 29 31] included both cross-sectional and longitudinal cohort studies. Two primary studies [19 20] were consistently included in all the seven reviews considered in Table II, one primary study [18] was included in six reviews, and two primary studies [23 38] were included in five reviews.

The first review providing an estimate of the association between cannabis and the subsequent development of psychosis was published by Arsenault et al. [25] The study included five cohort population based studies [14 18-20 23] and found that cannabis use confers an overall twofold increase in the relative risk for schizophrenia (pooled OR: 2.34; 95%CI 1.69 to 2.95) after adjusting for nearly thirteen possible confounders. The authors, while suggesting caution in interpreting their findings, concluded that about 8% of schizophrenia cases could be prevented by eliminating cannabis use in the population. In order to further investigate the consistency of association between cannabis and psychosis and estimate the overall effect size, Henquet et al. [26] carried out a meta-analysis from seven prospective studies [17-20 23 35 38]. In spite of differences in definition (some studies focused on the narrow outcome of schizophrenia, and others focused on the wider outcome of psychotic symptoms) and other differences among studies such as length of follow-up, the authors concluded that cannabis use increases the risk for psychosis (OR: 2.1, 95% CI: 1.7 to 2.5); this finding held regardless of whether it was considered only studies using the narrow clinical outcome (OR: 2.37, 95% CI: 1.7 to 3.3) or the broad outcome of psychotic symptoms (OR: 1.9, 95%CI 1.5 to 2.5). Semple et al. [27] reviewed five cohort [14 15 18-20] and 5 cross-sectional studies [45-49] looking at the association between cannabis and psychosis and found that cannabis is an independent risk factor for psychosis (pooled OR: 2.93, 95%CI 2.36 to 3.64). However, in the light of its major limitations (eg, inclusion of cross-sectional and longitudinal data, use of unadjusted estimates in the meta-analysis and combining effects for 'ever use' of cannabis with those for dependence), the authors concluded that the question of whether cannabis is a precipitating factor in vulnerable individuals or a causative agent remain unanswered. One of the most methodologically sound study was published by Moore et al. [28] who reviewed eleven studies drawn from five adult population-based cohorts [14 16 18 19 36 38 41] and two birth

Table I. Systematic reviews or narrative reviews with meta-analysis exploring the role of cannabis on the development of psychosis.

Author(s)	Year	Aim (s)	Type of paper
Arseneault et al. [25]	2004	To examine the evidence that cannabis causes psychosis by using established criteria of causality	Narrative review and meta-analysis
Macleod et al. [32]	2004	To review general population longitudinal studies relating illicit drug use by young people to subsequent psychological and social harm	Systematic review
Henquet et al. [26]	2005	To investigate the overall effect size and consistency of the association between cannabis and psychosis	Narrative review and meta-analysis
Semple et al. [27]	2005	To review case-control studies that clearly examined the association between cannabis use and schizophrenia or schizophrenia-like psychosis	Systematic review and meta-analysis
Moore et al. [28]	2007	To review longitudinal studies of cannabis use and subsequent psychotic outcomes, and to assess the strength of evidence that cannabis use and these outcomes are causally related	Systematic review and meta-analysis
Ben Amar and Potvin [29]	2007	To review current available data on relationship between cannabis and psychosis	Systematic review
Minozzi et al. [24]	2010	To summarize the findings of systematic reviews on the association between cannabis use and psychosis	Systematic review
McLaren et al. [33]	2010	To review methodological strengths and limitations of cohort studies which explored the link between cannabis and psychosis, and consider research findings against criteria for causal inference	Systematic review
Gage et al. [30]	2016	To review literature exploring the association between cannabis and psychosis	Narrative review and meta-analysis
Marconi et al. [31]	2016	To review studies investigating the association between cannabis use and psychosis and to quantify the magnitude of effect	Systematic review and meta-analysis

Study population	No. of studies	Time frame	Main findings
Adults	4 cohort studies, 1 longitudinal population-based study	n.s.	On an individual level, cannabis increase in the risk for schizophrenia (pooled OR: 2.34; 95%CI 1.69 to 2.95). At the population level, elimination of cannabis would reduce the incidence of schizophrenia by 8%
Adolescents	48 studies	Up to 2003	Inconsistent associations were found between cannabis use and both psychological health problems in adolescents (OR not reported). All these associations seemed to be explicable in terms of non-causal mechanisms
Adults	3 population-based, 1 conscript cohort and 3 birth cohort studies	n.s.	Cannabis is an independent risk factor for psychosis (pooled OR: 2.1, 95%CI 1.7 to 2.5) and could not be explained by confounding or reverse causality. Cannabis is a component cause in the development of psychosis, in which mechanisms of gene-environment interaction are most likely to explain this association
Adults and adolescents	4 cohort and 7 cross-sectional studies	Up to 2004	Cannabis is an independent risk factor for psychosis (pooled OR: 2.93, 95%CI 2.36 to 3.64). However, the question of whether cannabis is a precipitating or a causative factor in the development of schizophrenia remains
Adults	5 adult population-based cohorts and 2 birth cohort studies	Up to 2006	Cannabis use increases the risk of developing psychosis in people who had ever used cannabis (pooled OR: 1.41, 95%CI 1.20 to 1.65), with greater risk in those who used cannabis most frequently (OR: 2.09, 95%CI 1.54 to 2.84). At the population level, elimination of cannabis would reduce the incidence of any psychotic outcome by 14%
Adults	10 cohort studies	Up to 2005	Cannabis increases the risk of developing psychosis among vulnerable individuals and can negatively affect the course of preexisting chronic psychosis. This conclusion should be tempered by uncertainty arising from a series of methodological issues including the assessment of cannabis use, measurement of psychosis, reverse causality and control of other confounders
Adults	5 systematic reviews	Up to 2007	A consistent association between cannabis use and psychosis was found in the published reviews, though it is not possible to draw firm conclusions about a causal relationship
Adults	10 cohort studies	Up to 2008	Criteria for causal association between cannabis and psychosis are supported by the review. However, the issue of whether cannabis use can cause psychotic disorders that would not otherwise have occurred cannot be answered from the existing data
Adults and adolescents	10 cohort studies	n.s.	Cannabis increases the risk of developing psychosis (pooled OR: 1.46; 95%CI 5 1.24 to 1.72). Further studies are required to determine the magnitude of the effect, the effect of different strains of cannabis on risk, and to identify high-risk groups particularly susceptible to the effects of cannabis
Adults	6 cohort and 4 cross-sectional studies	Up to 2103	Cannabis use increases the risk of psychosis (OR: 1.97, 95%CI 1.68 to 2.31); a dose-response relationship between the level of use and the risk for psychosis was also found, since the risk doubled for heavy users (OR: 3.90, 95%CI 2.84 to 5.34)

Table II. Primary studies included in the systematic reviews/meta-analyses providing estimates for the risk of psychosis linked to cannabis use.

	Marconi et al. 2016	Gage et al. 2016	Moore et al. 2007	Ben Amar & Potvin, 2007	Henquet et al. 2005	Semple et al. 05	Arseneault et al. 2004
Cohort studies							
Andreasson et al., 1987 (Swedish conscript cohort) [14]			x			x	x
Andreasson et al., 1989 (Swedish conscript cohort) [15]						x	
Tien & Anthony, 1990 (ECA) [16]	x	x	x				
Weiser et al., 2002 [17]					x		
van Os et al., 2002 (NEMESIS) [18]		x	x	x	x	x	x
Zammit et al., 2002 (Swedish conscript cohort) [19]	x	x	x	x	x	x	x
Arseneault et al., 2002 (Dunedin birth cohort study) [20]	x	x	x	x	x	x	x
Philips et al., 2002 [22]				x			
Fergusson et al., 2003 (CHDS) [23]		x	x	x	x		x
Degenhardt et al., 2003 [34]				x			
Stefanis et al., 2004 [35]					x		
Zammit et al., 2004 (Swedish conscript cohort) [36]			x				
Caspi et al., 2005 (Dunedin birth cohort study) [37]			x				
Henquet et al., 2005 (EDSP) [38]	x	x	x	x	x		
Ferdinand et al., 2005 [39]				x			
Fergusson et al., 2005 (CDHS) [40]		x					
Wiles et al., 2006 (NPMS) [41]	x	x	x				
Zammit et al., 2011 (Swedish conscript study) [42]	x						
Rossler et al., 2012 [43]		x					
Gage et al., 2014 (ALSPAC) [44]		x					
Cross-sectional studies							
Rolfe et al., 1993 [45]						x	
Grech et al., 1998 [46]						x	
Degenhardt et al., 2001 [47]	x					x	
Agosti et al., 2002 [48]						x	
Farrel et al., 2002 [49]						x	
Miettunen et al., 2008 [50]	x						
McGrath et al., 2010 [51]	x						
Di Forti et al., 2014 (GAP data 2012) [52]	x						

cohorts [20 23 37 40]. The review found, after adjusting for a comprehensive list of confounding factors, a 40% increase in risk of any psychotic outcome in cannabis users (pooled OR: 1.41, 95%CI 1.20 to 1.65) and a stronger association with heavier or more regular cannabis use (OR: 2.1, 95%CI 1.5 to 2.8). The authors also reported that associations were unlikely to reflect reverse causality because all primary studies excluded people with psychosis at baseline. After the publication of this systematic review some new data have become available, all supporting the causal association between cannabis use and psychosis. Gage et al. [30] have recently updated the estimate provided by Moore et al. [28], by including adjusted results from the Zurich Study [43] and the Avon Longitudinal Study of Parents and Children [44] and found a very similar pooled odds ratio for any psychotic outcome of 1.46 (95%CI 1.24 to 1.72). More recently, Marconi et al. [31] published a new meta-analysis which examined ten studies, six prospective studies [16 19 20 38 41 42], three cross-sectional studies [47 50 51], and one case-control study [52] conducted in seven developed countries across three continents. The authors [31] found that cannabis use is associated with a dose-dependent increase in the risk of psychosis: the risk is doubled in the average user (OR: 1.97, 95%CI 1.68 to 2.31) and quadrupled in the heaviest users (pooled OR: 3.90, 95%CI 2.84 to 5.34). The study controlled for a number of confounders, including age, gender, ethnicity, nicotine smoking, lifetime exposure to drugs other than cannabis, education and employment status.

The reviews without a meta-analysis (see Table I) reported an inconsistent association between cannabis use and psychosis. Macleod et al. [32] reviewed sixteen longitudinal studies, only four of which specifically focusing on the association between cannabis use and psychosis [14 19 20 37] and concluded that the causal nature of this association is far from clear because of flaws in the primary studies: a dose-response relationship was difficult to assess because only binary exposure categories were examined in many of the studies, and the reverse causation hypothesis cannot be excluded because unreported or sub-clinical problems might have preceded cannabis use, even in studies that adjusted for psychological symptoms at baseline. According to the authors [32], it is possible that cannabis use and psychosis might share common antecedents, and that the relationship between cannabis use and psychosis could simply reflect this association. Ben Amar and Potvin [29] reviewed ten longitudinal studies and found that three of them supported a causal relationship between cannabis use and psychosis [14 18 19]; five suggested that chronic cannabis intake increases the frequency of psychotic symptoms, but not of diagnosed psychosis [20 23 38 39 40]; and two showed no causal relationship [22 34]. The authors concluded that although there is evidence that cannabis use increases the risk of developing psychotic symptoms, the causal nature of this association remains unclear; if cannabis use is assumed to be a component cause of a complex series of conditions leading to psychosis or psychotic symptoms, then some factors contributing to this phenomenon might include heavy consumption of cannabis, length of exposure to this drug, early age of first use and psychotic vulnerability. McLaren et al. [33] reviewed the methodological strengths and limitations of ten studies from seven general population cohorts [14 16 18 19 23 37 38 41] which explored the link between cannabis and psychosis and considered research findings against criteria for causal inference. The authors [33] indentified a number of limitations in the studies reviewed, specifically definition of psychosis, consideration of the short-term effects of cannabis intoxication, control of potential confounders and measurement of drug use during the follow-up period. This study [33] confirms that whilst the criteria for causal association between cannabis and psychosis are supported by the studies reviewed, the contentious issue of whether cannabis use can cause serious psychotic disorders that would not otherwise have occurred could not be answered from the existing data. The authors seem rather to suggest that pre-existing vulnerability to psychosis is as an important factor that influence the link between cannabis use and psychosis.

Narrative reviews on the effect of cannabis on the onset of psychosis

Narrative reviews exploring the role of cannabis on the development of psychosis are summarized in Table III.

Based on the available evidence (i.e., the primary studies listed in Table II), most of the narrative reviews published on this topic came to the conclusion that early and heavy cannabis use increases the risk of psychosis in people with genetic/biological vulnerability [1 13 53-64] and that the association is independent from potential confounding factors [54-57 61]. The risk of developing a long lasting psychotic condition is particularly high if the exposure to cannabis starts early in adolescence [65-69]. However, these reviews also indicate that cannabis by itself it is neither a sufficient nor a necessary cause of psychosis. Most of these reviews also indicate that the

Table III. Narrative reviews exploring the role of cannabis on the development of psychosis.

Author(s)	Year	Aim (s)	Type of paper	Study population
Johns [53]	2001	To review the adverse effects of cannabis in the general population and among vulnerable individuals	Narrative review	Adults
Hall and Degenhardt [74]	2000	To evaluate evidence for two hypotheses: (1) cannabis use causes psychosis; (2) cannabis use may precipitate psychosis or exacerbate symptoms	Narrative review	Adults
Degenhardt and Hall [75]	2002	To discuss reasons for the association between cannabis and psychosis by considering the main hypotheses proposed to explain this association	Narrative review	Adults
Smit et al. [54]	2004	To review the role of cannabis use in the onset of symptoms and disorders in the schizophrenia spectrum	Selective review	Adults
Rey et al. [55]	2004	To critically review cannabis research over the last 10 years in relation to rates of use and mental disorders in young people	Narrative review	Adolescents
Hall et al. [76]	2004	To evaluates the existing hypotheses about the relationship between cannabis use and psychosis in the light of recent evidence from prospective studies	Narrative review	Adults
Verdoux and Tournier [56]	2004	To clarify the nature of the link between cannabis use and psychosis	Narrative review	Adults
Verdoux et al. [57]	2005	To examine the impact of substance use on the onset and course of early psychosis	Narrative review	Adults and adolescents
de Irala et al. [71]	2005	To critically analyze the public health relevance of available evidence about the causal relationship between cannabis use and psychosis	Narrative review	Adults and adolescents
Degenhardt and Hall [77]	2006	To assess whether cannabis use in adolescence and young adulthood is a contributory cause of psychosis in that it may precipitate psychosis in vulnerable individuals	Narrative review	Adults and adolescents
Murray et al. [1]	2007	To outline recent research into the endocannabinoid system and to consider the evidence as to whether cannabis can induce acute and chronic psychosis	Narrative review	Adults
Cohen et al. [58]	2008	To review the links between cannabis use and psychosis, drawing upon recent epidemiological, clinical, cognitive, brain imaging and neurobiological research	Narrative review	Adults
Rubino and Parolaro [65]	2008	To examine the existing literature on the long-term consequences of cannabis exposure during adolescence	Narrative review	Adolescents
Henquet et al. [70]	2008	To consider the interplay between genes and exposure to cannabis in development of schizophrenia	Narrative review	Adults
De Lisi [72]	2008	To explore what is known about cannabis's association with schizophrenia, cannabis's effects on the brain, and whether the brain changes present in schizophrenia could be caused by cannabis	Narrative review	Adults
Tucker [59]	2009	To review current knowledge about the relationship between substance misuse and early psychosis	Narrative review	Adults

No. of studies	Time frame	Main findings
n.s.	n.s.	Heavy cannabis use leads to risk of psychotic episode and aggravates the symptoms and course of schizophrenia
n.s.	n.s.	Evidence supports the hypothesis that cannabis use precipitates schizophrenia in persons who are vulnerable because of a personal or family history of schizophrenia or exacerbates the symptoms of schizophrenia
n.s.	n.s.	Evidence suggests that cannabis use may precipitate psychosis among vulnerable individuals, increase the risk of relapse among those who have already developed the disorder, and may be more likely to lead to dependence in persons with schizophrenia
5 longitudinal population-based studies	n.s.	Evidence suggests that cannabis is an etiological cause of psychosis. Cannabis use roughly doubles the risk of becoming schizophrenic; the risk increases when more cannabis is used and in vulnerable people
	1994-2004	Growing evidence suggests that early and regular cannabis use is associated with later increases in depression, suicidal behavior, and psychotic illness and may bring forward the onset of schizophrenia
n.s.	n.s.	It is unlikely that cannabis use can produce psychoses ; cannabis use, however, can precipitate schizophrenia in vulnerable individuals because of a personal or family history
	n.s.	Cannabis exposure is associated with an increased risk of psychosis, possibly by interacting with a pre-existing vulnerability; a dose-response relationship was found and this association was independent from potential confounding factors
n.s.	n.s.	Longitudinal studies found a dose-response relationship between cannabis exposure and risk of psychosis; this association is independent from potential confounding factors
n.s.	n.s.	There are conflicting views about causal relationship. However, the most sensible public health action should be to give counseling against cannabis use to all adolescents, similarly to what is currently being done to prevent the use of tobacco or alcohol
n.s.	n.s.	Regular cannabis use predicts an increased risk of schizophrenia and this relation persists after controlling for confounding variables. It is likely that cannabis use precipitates schizophrenia in individuals who are vulnerable because of a personal or family history of schizophrenia
n.s.	n.s.	Epidemiological evidence strongly suggests that heavy cannabis use increases the risk of both psychotic symptoms and schizophrenia. Cannabis acts as a component cause that increases the risk of psychotic illness between 1.4 and 1.9 times, and that might account for between 8 and 14% of cases of schizophrenia in different countries
n.s.	n.s.	Cannabis use increases the risk of psychosis by 40%; approximately 14% of psychotic outcomes in young people would not have occurred if cannabis had not been consumed
n.s.	n.s.	Pubertal cannabis use in vulnerable individuals may act as a risk factor for inducing enhanced behavioral disturbances related to schizophrenia
n.s.	n.s.	Mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis. Multiple variations within multiple genes, together with other environmental factors (eg, stress), may interact with cannabis to increase the risk of psychosis
n.s.	n.s.	The evidence from epidemiological studies is inconsistent and not conclusive that cannabis causes schizophrenia and thus the issue is still highly controversial. Further research is needed to determine the biological effect that cannabis has on the brain in people who do or do not develop schizophrenia
n.s.	n.s.	Cannabis appears to confer increased likelihood of developing schizophrenia in biologically vulnerable individuals

follows

continue Table III

Author(s)	Year	Aim (s)	Type of paper	Study population
Sewell et al. [60]	2009	To review the evidence supporting and refuting the association between cannabis exposure and psychotic disorders	Narrative review	Adults
D'Souza et al. [61]	2009	To review clinical and preclinical studies investigating cannabis use as a risk factor for the development of psychosis	Narrative review	Adults
Shapiro and Buckley-Hunter [66]	2010	To explore the relationship between cannabis and the onset of psychosis	Narrative review	Adults and adolescents
Gururajan et al. [62]	2012	To review clinical and preclinical studies investigating cannabis or methamphetamine use as a risk factor for the development of psychosis	Narrative review	Adults
Rubino et al. [67]	2012	To review clinical and preclinical studies investigating cannabis use as a risk factor for the development of psychiatric disorders in adolescents	Narrative review	Adolescents
Parakh and Basu [63]	2013	To review studies exploring the association between cannabis use and psychosis	Narrative review	Adults
Burns [64]	2013	To examine causality, the neurobiological basis for such causality and for differential inter-individual risk, the clinical and cognitive features of psychosis in cannabis users	Narrative review	Adults
Gage et al. [73]	2013	To consider the evidence for a causal relationship between cannabis use and psychosis and to discuss the issue in a public health perspective	Narrative review	Adults and adolescents
Radhakrishnan et al. [68]	2014	To review existing literature on the association between cannabis and psychosis	Narrative review	Adolescents
Wilkinson et al. [69]	2014	To review the evidence investigating the association between cannabis and psychotic disorders with special attention to literature from the past three years	Narrative review	Adults and adolescents
Volkow et al. [13]	2014	To review the current state of the science related to the adverse health effects of the recreational use of cannabis, focusing on those areas for which the evidence is strongest	Narrative review	Adults and adolescents
Ksir and Hart [78]	2016	To review research on cannabis and psychosis, with specific emphasis to how studies provide evidence relating to the hypothesis of (1) cannabis as a contributing cause, and (2) shared vulnerability	Narrative review	Adults and adolescents
Volkow et al. [13]	2016	To identify what is known and not known about the effects of cannabis use on human behavior, including cognition, motivation, and psychosis	Narrative review	Adults and adolescents

ECA: Epidemiological Catchment Area study (USA); NEMESIS: Netherlands Mental Health Survey and Incidence Study (NL); CHDS: Christchurch Health and Development Study (New Zealand); EDSP: Early Developmental Stages of Psychopathology (Germany); NPMS: National Psychiatric Morbidity Survey (UK); GAP: Genetics and Psychosis study (UK); ALSPAC: Avon Longitudinal Study of Parents and Children (UK).

No. of studies	Time frame	Main findings
n.s.	n.s.	Cannabis use is a component cause that may induce psychotic disorders. However, cannabis is neither necessary nor sufficient to do so alone. Further work is needed to identify the factors that underlie individual vulnerability to cannabis and to elucidate the biological mechanisms underlying this risk
n.s.	n.s.	Early and heavy cannabis use may increase the risk of developing psychosis. However, the mechanisms by which exposure to cannabis increase the risk for psychosis are unknown and warrants further research
n.s.	n.s.	Cannabis is a significant risk factor in the etiology of psychosis; adolescents are more vulnerable to using cannabis
n.s.	n.s.	Literature support the existence of causation between cannabis and schizophrenia. However, further studies are needed to provide a greater insight into the mechanisms that mediate the long-term and neurodevelopmental effects of cannabis
n.s.	n.s.	Early cannabis use in adolescence is closely related to increased risk of later psychiatric problems (cognitive abnormalities, psychosis, mood disorders), especially in vulnerable people. Further studies are needed to clarify the mechanisms underlying the effect of cannabis on the adolescent brain
n.s.	n.s.	Cannabis use increases the risk of psychosis in people with genetic or environmental vulnerability. However, cannabis by itself it is neither a sufficient nor a necessary cause of psychosis
n.s.	n.s.	Early-initiated, lifelong cannabis use in vulnerable individuals may lead to a psychosis virtually indistinguishable from schizophrenia at onset. In those whose cannabis use persists, a chronic deteriorating disorder seems to follow (in these cases one may conclude that cannabis has been played a causal role). Recent use of cannabis in vulnerable individuals, just prior to psychosis onset, is clinically distinguishable from schizophrenia at first-episode; ceasing cannabis use after the first-episode have an excellent prognosis with full recovery
n.s.	n.s.	Consistent evidence shows that individuals who use cannabis have an increased risk of psychotics. However, the role of cannabis in the aetiology of schizophrenia remains uncertain given the limits of observational epidemiology
n.s.	n.s.	Exposure to cannabis in adolescence confers a higher risk for psychosis in later life and the risk is dose-related
n.s.	2011-2013	Exposure to cannabis in adolescence is associated with a risk for later psychotic disorder in adulthood; this association is consistent, temporally related, shows a dose-response. However, cannabis is neither necessary nor sufficient to cause a persistent psychotic disorder; it is probably a component cause that interacts with other factors
n.s.	n.s.	Cannabis use is associated with onset of psychosis, especially among people with a preexisting genetic vulnerability, and exacerbates the course of illness in patients with schizophrenia. However, it is difficult to confidently attribute the increased risk of psychosis to cannabis use
n.s.	n.s.	Cannabis does not in itself increase the risk for psychosis; evidence seems to suggest that both early use of cannabis and heavy use of cannabis are more likely in individuals with a vulnerability to a variety of other problem behaviors; the same vulnerability also results in increased risk for psychosis or some other mental disorder in some individuals
n.s.	n.s.	Prospective, longitudinal, epidemiological studies consistently report an association between cannabis use and schizophrenia. While cannabis use is neither necessary nor sufficient for the development of schizophrenia, available evidence suggests that cannabis use may initiate the emergence of a lasting psychotic illness in individuals with a genetic vulnerability

mechanisms by which exposure to cannabis increase the risk for psychosis are stills unknown and warrants further research [60-63]. Mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis. Multiple variations within multiple genes, together with other environmental factors (eg, stress), may interact with cannabis to increase the risk of psychosis [70].

Other reviews are more cautious in attributing the increased risk of psychosis to cannabis use [13]. According to some authors the evidence from epidemiological studies is still inconsistent and not conclusive [71-73]. It seems unlikely that cannabis use can produce psychoses, it is more likely that cannabis use precipitates psychosis in individuals who are vulnerable because of a personal or family history [74-77]. Ksir and Hart [78] maintain that cannabis does not in itself increase the risk for psychosis; they rather suggest that both early use of cannabis and heavy use of cannabis are more likely in individuals with a vulnerability to a variety of other problem behaviors (the same vulnerability also results in increased risk for psychosis or some other mental disorder in some individuals). All these authors, however, consistently suggest that further research is needed to better understand the associations between cannabis and psychosis and the possible mechanisms underlying this association.

Effect of cannabis on transition to psychosis in clinical high risk populations

People at clinical high risk for psychosis represent an ideal population in which to investigate the putative role of cannabis use in the onset of psychosis, as 20-35% will develop the disorder within a few years following clinical presentation [79]. So far three systematic reviews on studies exploring the effect of cannabis use on transition to psychosis in clinical high risk individuals have been published. Their main results are summarized in Table IV.

The first review [80], included eleven studies, reported mixed results: some research found that cannabis use was associated with more severe symptoms at baseline, increased pre-psychotic symptoms immediately after intoxication, and earlier onset of certain high-risk symptoms, whereas other studies did not report any significant association between cannabis use and baseline symptoms. Four out of five studies reported no significant effect of cannabis use on transition to psychosis. The second review [81] reported that the majority primary studies did not found a role for cannabis use in later conversion to psychosis: among the ten studies reviewed only two reported a significant association between lifetime cannabis use and transition to psychosis [82 83]. More recently, Kraan et al. [84], in a systematic review and meta-analysis of seven prospective studies with a follow-up duration of 1-4 years, reported that lifetime cannabis use was not significantly associated with transition to psychosis (OR: 1.14, 95%CI 0.86 to 1.52); however, current cannabis abuse or dependence were associated with increased risk of transition into psychosis in subjects at ultra high risk of psychosis (OR: 1.75, 95%CI 1.135 to 2.71). The major limitation of literature examining the impact of cannabis use on transition to psychosis is the lack of control for potentially confounding factors. Some of the potential control factors would include method of ascertainment of subjects, inclusion and exclusion criteria particularly, age of participants which typically vary from 12 to 31, age at first use of substances particularly cannabis, assessment of substance use which should include type and quantities and possibly biological measures, co-morbid diagnoses (e.g. mood disorders), medications including antipsychotics and other potential risk factors such as family history. Inconsistencies found in this literature

Table IV. Systematic reviews exploring the role of cannabis on the transition to psychosis in at-risk populations.

Author(s)	Year	Aim(s)	Type of paper	Study population
van der Meer et al. [80]	2012	To review studies measuring the impact of cannabis use on CHR symptoms and transition to a first psychotic episode	Systematic review	Adolescent (Clinical High Risk)
Addington et al. [81]	2014	To review studies measuring patterns and rates of substance use in CHR individuals and the effects on the transition to psychosis	Systematic review	Adolescent (Clinical High Risk)
Kraan et al. [84]	2016	To understand the role of cannabis use on transition to psychosis in UHR individuals	Systematic review and meta-analysis	Adolescent (Ultra High Risk)

highlight the need for further work in clinical high risk samples in order to understand the role of cannabis use in the onset of psychosis. Future work investigating cannabis use in the clinical high risk group should seek to determine, through repeated assessment of substance use alongside other potential risk factors and multiple outcomes, the interplay between cannabis, pre-existing vulnerability for psychosis, and symptom expression in the onset of psychosis.

Discussion

Main findings

Most of the systematic reviews considered in this paper consistently report a significant association between cannabis use and psychosis which could be indicative of a causal relationship [25-29 31], or at least suggest that the possibility of such a relationship cannot be excluded [30 32]. Overall, people using cannabis have at least a two-fold risk of developing psychosis compared to people who do not use it [25-31] and the risk is increased (at least four-fold) among the heaviest users [28-31].

However, the primary cohort studies considered in these reviews have a number of methodological limitations and therefore caution should be used when interpreting results. The first published systematic review of cannabis use and psychosis included cross-sectional studies and did not address study quality [27]. Another systematic review examined broader psychosocial outcomes, but the lack of focus specifically on psychotic disorders meant that the explanations for associations could not be examined in detail [32]. Early meta-analyses from both systematic [27] and narrative [25 26] reviews included cross-sectional data [25 26] or used unadjusted results [27] and combined effects for ever-use of cannabis with those for dependence [25-27]. As might be expected, all report larger effects than observed in Moore et al. [28] and, more recently, in Marconi et al. [31], although direct comparison of these effects is difficult.

There is also indirect evidence that supports causality. For example, a number of primary studies [18-20] included in the reviews considered here found evidence for specificity of exposure, namely that associations between other drug use and psychosis are weaker than for cannabis. There is also some evidence of specificity of outcome [28], though this is not seen in all studies [30]. Research has also shown that associations between cannabis use and psychotic symptoms are not reducible to family history of psychosis [14 15 18 28 31] and – most important – that genetic liability for psychotic disorder does not predict cannabis use [85]. However, even if the association between cannabis and psychosis is causal, cannabis is neither necessary nor sufficient to cause psychotic disorder; risk factors for multifactorial complex disorders, such as psychosis, are not deterministic and in this context cannabis may be seen as "a component cause" for the development of psychotic disorder or psychotic symptoms [86].

The role of genetic predisposition

As cannabis use is neither necessary nor sufficient for the development of psychosis, it has been suggested that cannabis may induce the onset of enduring psychotic disorders in individuals with a genetic vulnerability. Mechanisms of gene-environment interaction are likely to underlie the association between cannabis and psychosis: Caspi et al. [37] found that cannabis use during adolescence was associated with an increased risk of developing psychosis during adulthood among individuals carrying the COMT Val/Val genotype, to a lesser extent among Val/Met individuals, but not among Met/Met individuals. These cannabis x COMT

No. of studies	Time frame	Main findings
11 studies	Up to 2011	Cannabis use seems to provoke and enhance subclinical symptoms in CHR subjects. However, the results provide no consistent evidence for an association between cannabis use and transition to a first psychosis in CHR subjects
10 studies	Up to 2013	Limited evidence was found to suggest that increased rates of substance use may be associated with transition to psychosis. However, further prospective research examining the association between substance use and transition to psychosis is required before any firm conclusions can be made
7 cohort studies	Up to 2015	Cannabis use is predictive of transition to psychosis only in those meeting criteria for cannabis abuse or dependence (OR 1.75, 95% CI 1.13 to 2.71), thus suggesting a dose-response relationship between current cannabis use and transition to psychosis

Val158Met interactions were replicated in several [78 87-90], but not in all studies [42 91 92]. The results supporting the hypothesis that some gene variants influence the likelihood of developing schizophrenia contingent on certain environmental exposure (eg, cannabis use) reflect tentative findings among small numbers of individuals that require replication [93]. Alternatively, Ksir and Hart [78] suggest that both psychosis and cannabis use are more likely in individuals with a shared vulnerability to misuse of various substances and increased risk for various mental disorders. In other words, the correlation between cannabis use and psychosis is not specific, either with regard to the chemicals found in cannabis or to psychosis as opposed to other disorders. However, two recent GWAS studies [94 95] suggest that the overlap in genetic vulnerability for psychosis and cannabis use is likely to be only modest. Thus, should there be any shared genetic vulnerability between cannabis use and schizophrenia, it could explain only a small proportion of the association between the two [96].

Some criticisms to causal explanation

One argument against cannabis having a causal role in psychosis is that cannabis use became more common in the latter part of the 20th century without an obvious change in the incidence of schizophrenia [21]. There is little reliable evidence on temporal trends in the incidence of schizophrenia and related psychoses, so it is difficult to establish whether this statement is true or not. Some studies reported that incidence of schizophrenia and related psychosis has increased in recent decades [97], while others have found no change or a decrease [98-100]. Ecological studies provides only very weak evidence for causality, as it cannot be ascertained whether individuals using cannabis are the same as those experiencing psychosis (the ecological fallacy); moreover these studies are unable to account for likely confounders, and do not account for other potentially competing risk factors for schizophrenia that may have declined over the same time period [30]. Whether preventing cannabis use will have any substantial impact on preventing psychotic disorders in the population, or within specific subgroups at risk, is yet to be adequately determined [73]. What we do know is that the incidence of schizophrenia and other related psychosis is significantly higher in countries such, as England [101] and The Netherlands [102], where high potency cannabis has taken over the market [103] compared with other countries, such as Italy [104 105], where more traditional forms of cannabis are smoked [106].

High potency cannabinoids

The use of high potency cannabis is currently widespread across some European countries and represents a critical issue. The cannabis plant produces at least 80 chemicals, and the two best known (THC and cannabidiol [CBD], a cannabinoid that seems to offset some of the adverse effects of THC) vary not only in their strength but also in their ratio in different types of cannabis. Over the last 5 decades, selective breeding has increased the concentration of THC in the cannabis available in many countries. For example, the THC content of cannabis in the 1960s in England and The Netherlands was around 3%; high potency varieties now available average 16% in England [107] and 20% in The Netherlands [108]. Furthermore, traditional hash (resin) contains THC and a similar proportion of CBD, but new varieties ('skunk') have high levels of THC, but practically no CBD [86]. Recent research conducted in England found that people using high-potency cannabis on a daily basis are five times more likely than non-users to suffer from a psychotic disorder [109]. This finding has increased concern that as levels of THC in cannabis have altered over the past few decades, results from earlier studies could be underestimating the impact of the effects of cannabis on psychosis that exist today.

A public health perspective

If the overall rate of schizophrenia in the population is about 1% and if the association between cannabis and schizophrenia is causal and of the magnitude estimated across studies to date [28 31], this would equate to a schizophrenia lifetime risk of approximately 2-3% in regular cannabis users (though risk for broader psychotic outcomes will be greater). The risk could be much greater in those at a higher genetic risk [110] or in those who use high-potency cannabis [109]: if regular cannabis use increased the risk of schizophrenia twofold and assuming the pattern of risk for co-exposure to cannabis and high genetic risk is approximately multiplicative, as it is for most risk factors for multifactorial complex disorders, then the lifetime risk in individuals with a first-degree relative if they use cannabis regularly could be around 20%. This is a cause of concern for mental health care provision. Given the potential of millions of new cannabis users, the above mentioned estimates translate into several thousands of individuals with quite disabling psychotic symptoms at a time when mental health services, in most European countries are facing a major crisis due to a dramatic reduction in funding and resources.

There remains argument over the proportion of psychosis that could be prevented if nobody used cannabis. The population attributable fraction (PAF) measures the population effect of an exposure by providing an estimate of the proportion of disorder that would be prevented, assuming casualty, if the exposure was removed. The PAF depends on both the prevalence of exposure (ie, measures of cannabis use) in cases and the odds ratio (OR) for the exposure, such that a risk factor with a modest OR can have a major population effect if the exposure is common. Estimates of the PAF suggest that from 8 to 24% of psychosis in different countries could be prevented if cannabis use was prevented, depending on whether risk is confined to heavy cannabis or all users. The PAF for the Dunedin study in New Zealand [25] was 8%. Henquet et al. [26] calculated that the PAF for individuals in the general population in Germany with a predisposition for psychosis was more than double (14%) that of the total population (6%). Moore et al. [28], based on the proportion of adolescents and young adults in the UK who have ever used cannabis (40%) and on the risk of a psychotic outcome for having ever used cannabis, estimated that about 14% of psychotic outcomes in young adults would not occur if cannabis were not consumed. More recently, Di Forti et al. [109] reported an increased estimate for the PAF accounted for by cannabis (24%) compared with previous studies; this finding could be caused by, not only the greater use of cannabis, but also the greater use of high-potency ('skunk') cannabis in south London. All such estimates, however, rely on the assumption that the association between cannabis use and psychosis is causal, and that the relative risk is an accurate estimate of this causal effect.

Policy implications

A causal relationship between cannabis use and psychotic disorders may not be still proven 'beyond reasonable doubt', but in the absence of any specification of plausible uncontrolled confounders there are good reasons for believing that cannabis is much more likely than not to be a contributory cause of these disorders. The epidemiological evidence and the biological plausibility of the relationship are strong enough to warrant giving advice to young people about this possible risk, along with information on other potential adverse effects of cannabis. The potential effects of a psychotic illness on a young person's life chances are so substantial that it would be socially irresponsible not to do so [111].

How strong must the evidence for a causal relation between cannabis and psychosis be before taking action would be justified? If the standard of proof we require for action is 'beyond reasonable doubt', then we would find it difficult to make any policy decisions according to the available evidence. If, however, we are prepared to act on the balance of probabilities (more likely than not), some policy action is warranted [112]. Prevention is better than treatment. In this regard, it is worth recalling the many years it took for cigarette smoking to be accepted as a cause of lung cancer and that 4 decades passed before serious attempts were made to persuade people to stop smoking tobacco [86]. By the same sort of prudential reasoning, it would be arguably good social policy to encourage young people to avoid using cannabis or, at the least, to delay their use into early adulthood [71]. Young adolescents seem more vulnerable to the effects of cannabis. The Dunedin cohort study [20] found a stronger association between cannabis use and the development of psychotic symptoms among individuals who first used cannabis before the age of 16. These observations could be related to the fact that cannabis is particularly harmful to the brain during its critical period of development earlier in adolescence [65 67 68]. An early age of exposure to cannabis is a contributing factor to the precocious onset of a first psychotic episode, as confirmed by the meta-analysis of Large et al. [113] which found an earlier age at onset of psychosis (nearly three years) in people using cannabis compared to non users. The same research group also found that the effect of cannabis is specific, since other substances such as alcohol or tobacco are not associated with a younger age at onset of psychosis [114]. Thus reducing the use of cannabis could be one of the few ways of altering the outcome of psychosis because earlier onset is associated with a worse prognosis and because other factors associated with age at onset, such as family history and sex, cannot be changed [115]: an extra two or three years of psychosis-free functioning could allow many patients to achieve the important developmental milestones of late adolescence and early adulthood that could lower the long-term disability arising from psychotic disorders [113]. For the above mentioned reasons it makes a good case to discourage cannabis use amongst young people, whilst there is room for disagreement about what the best means of achieving this goal are [32 112].

Conclusions

Recent changes to cannabis legislation in some states of the USA will provide a number of natu-

ral experiments of both the risks and benefits of decriminalizing marijuana and legalizing the supply of cannabis [86]. The next decade will provide an opportunity to document both the benefits and risks associated with the changing legal landscape regarding cannabis use. Given the emerging evidence concerning the adverse effects of cannabis use, and the fact that the legalization of the drug could arguably increase the level of risk posed by cannabis use, it is critical that these changes in cannabis legislation are monitored and evaluated through well-designed studies that are able to assess the impact of these law changes both at individual and population levels [116].

Further steps to legalize cannabis use will inevitably lead to increased availability, thereby facilitating increased use, perhaps among individuals that might not have tried cannabis otherwise. Although current scientific evidence may not be sufficient to support a complete public policy reversal on cannabis, it should cause concern among policy makers, health care professionals, and educators.

Take home messages for psychiatric care

- Cannabis use is causally associated with at least a two-fold risk of developing psychosis
- The risk is further increased in people with genetic/biological vulnerability, who start using cannabis early in adolescence and who heavily use cannabis (or use high potency cannabis)
- Cannabis by itself it is neither a sufficient nor a necessary cause of psychosis (it is rather a component cause)
- Cannabis use should be discouraged among young people and subjects vulnerable to psychosis

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WHAT IS THE ROLE OF CYP GENOTYPING IN PSYCHIATRY?

Abstract
Aim of this article was to summarize the available evidence on the role of genetic variants of the cytochrome P450 (CYP) enzyme system in the metabolism and clinical response to the most commonly used psychotropic drugs. The clinical implications of CYP genotyping procedures in psychiatry were also critically evaluated. Genetic polymorphisms of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 have been reported to cause large interindividual differences in the serum concentrations of many drugs used in psychiatry, in particular antidepressants and antipsychotics. However, the influence of CYP variants on pharmacokinetic parameters of psychotropic drugs has not been associated so far with consistent results on a clinical level, that is, in terms of therapeutic effect and adverse events. Genotyping for allelic variants of CYP2D6 and CYP2C19 can be used to personalize dosing for outliers, i.e., poor metabolizers or ultrarapid metabolizers. Recommendations from practice guidelines describing CYP2D6 and CY2C19 genotyping for dosing some antidepressants and antipsychotics have been recently developed. Genotyping for CYP2D6 and CYP2C19 is currently performed only when issues relating to efficacy, such as non-response, or safety, such as severe adverse effects, occur. In order to better personalize treatment in psychiatry, the best approach is to integrate CYP2D6 and CYP2C19 genotyping and therapeutic drug monitoring (TDM). At present, genotyping for CYP1A2, CYP2B6, CYP2C9 and CYP3A4 may be of interest in an academic context, but has limited clinical utility in psychiatry.

Key words: Cytochrome P-450 enzyme system, pharmacogenetics, psychotropic drugs, genotyping.

Introduction

Psychiatric disorders are a leading cause of disability worldwide and despite important pharmacological advances, are still difficult to diagnose and treat. As with most therapeutic agents, clinical response to psychotropic drugs varies considerably among patients treated with the same dose: from no response at all to severe adverse drug reactions (ADRs). In addition to psychological and social implications, this variability results from the interaction of genetic, personal (e.g., age, sex, diseases) and environmental (e.g., smoking, diet, alcohol habits, concomitant medications) factors that produce interindividual differences in pharmacokinetics and pharmacodynamics [1].

Pharmacogenetics is the discipline studying the genetic basis leading to individual variation in drug response [2]. Genetic factors may influence drug response at the level of drug-metabolizing enzymes, drug transporters, drug targets and other biomarker genes [3]. One of the man goals of modern drug therapy has been the identification of these gene variants. This has been frequently described as “individualized” or “personalized medicine”. On the other hand, the term pharmacogenomics has a broader meaning and consists of the study of the entire spectrum of

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genes that determine drug response, including the assessment of the diversity of human genome sequence and its clinical consequences [2].

Genetically determined variability in drug metabolism may result in interindividual differences in the pharmacokinetics and plasma/serum concentrations of a given drug. Over the past decades, several polymorphisms associated with drug metabolism have been identified [3]. As most psychotropic agents undergo extensive hepatic metabolism, predictable variations in genes encoding drug-metabolizing enzymes may account for differences in drug efficacy and safety in psychiatric disorders [4].

The present article reviews the available evidence illustrating the role of genetic variants of the cytochrome P450 (CYP) enzyme system, the most important phase I drug-metabolizing enzymes, in the pharmacokinetics and clinical response to the most commonly used psychotropic drugs and critically evaluates the implications of CYP genotyping techniques in psychiatry. Articles for this review were obtained from a PubMed search with no time limit. Only articles published in peer-reviewed journals were included, while meeting abstracts were excluded.

The cytochrome P450 (CYP) enzyme system

Most psychotropic medications are highly lipophilic substances and therefore undergo significant biotransformation in the liver. Hepatic metabolism converts non-polar (lipid soluble) drugs into one or polar (hydrophilic) metabolites, this facilitating their elimination in urine or bile. The metabolism of psychotropic drugs involves phase I oxidative reactions, catalyzed via CYP enzymes, followed by phase II glucuronide conjugation, which occurs through UDP-glucuronosyltransferases (UGT) [5].

The CYP system consists of a superfamily of more than 50 heme-containing mono-oxygenases, located in the membranes of the smooth endoplasmic reticulum in the liver and in many extrahepatic tissues, which are responsible for the phase I oxidative reactions of many drugs, nutrients, environmental toxins and endogenous substances (i.e., steroids, fatty acids, prostaglandins) [3 6]. Interestingly, these enzymes are also expressed in the brain suggesting a role in the regulation of physiological homoeostasis by biotransformation of endogenous substrates [7]. They are classified into families and subfamilies according to similarities in their amino acid sequence, with each enzyme being designated as CYP followed by a number indicating the family, a letter indicating the subfamily, and another number denoting the specific isoform [8]. The human genome comprises 57 CYP genes divided into 18 families and 44 subfamilies according to sequence homology. The CYP 1 to 3 families are involved in phase I drug metabolism, whereas CYPs 4 to 51 are associated with endobiotic metabolism [3 8]. CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 are the isoforms which play a major role in the metabolism of therapeutic agents [3 6]. Other CYP isoforms contributing to drug metabolism include CYP2A6, CYP2C8 and CYP2E1. Each CYP isoform is a specific gene product and possesses a characteristic but relatively broad spectrum of substrate specificity. The greater part of CYP isoforms metabolize several drugs and the majority of drugs are metabolized by more than one CYP isoform. There is a significant variability in the expression and activity of CYP isoenzymes as a result of genetic, but also environmental factors.

The human CYP genes are highly polymorphic. A genetic polymorphism is defined as a stable variation in a given locus of the genetic sequence, which is detected in 1% or more of a specific population [2]. These polymorphisms reflect gene insertions and deletions, gene duplications, copy number variations, and single nucleotide polymorphisms (SNPs). Mutations or polymorphisms in genes coding for CYP isoforms can result in enzyme variants with higher, lower or no activity, or occasionally the total absence of the enzyme. These variants may explain a large portion of the manifold interindividual variability in drug metabolism and, therefore, can lead to differences in plasma/serum concentrations and therapeutic response to the administered medications. According to Ingelman-Sundberg et al. [3], the phenotypes associated with these genetic variants may be classified into four major groups:

- the poor metabolizers (PM), lacking functional enzymes due to defective or deleted genes;
- the intermediate metabolizers (IM), usually carrying 1 functional and 1 defective allele, but may also carry 2 partially functional alleles;
- the extensive metabolizers (EM), carrying 2 functional genes;
- the ultrarapid metabolizers (UM), with more than 2 active genes encoding a certain P450.

The activity of CYP enzymes can be evaluated by the use of phenotyping and/or genotyping tests [9]. Phenotyping procedures require the administration of a single dose of a probe compound to an individual, followed by quantification of urinary or serum concentrations of the drug and its major metabolite(s). The ratio of parent drug/ metabolite (metabolic ratio, MR) can be considered a proxy of activity of the enzyme respon-

sible for the formation of that metabolite and is often used to describe an individual's phenotype. Test drugs for in vivo phenotyping of CYP isoenzyme activity include the following: caffeine for CYP1A2, bupropion for CYP2B6, tolbutamide for CYP2C9, omeprazole for CYP2C19, dextromethorphan for CYP2D6 and midazolam for CYP3A4 [10]. Genotyping on the other hand is effected out through molecular genetic testing. This allows the detection and characterization of allelic variants for the genes coding for the polymorphic enzymes. The main advantage of a genotyping test is that it represents a trait marker which is not influenced by environmental factors. The test can be performed in any situation and its result lasts a lifetime.

The clinical significance of a CYP polymorphism is related to a number of factors, such as the pharmacological and toxic activity of the parent compound and/or its metabolite(s), the therapeutic index of the drug and the overall contribution of the polymorphic pathway to the total clearance of the drug. The clinical consequences of polymorphic genes for drug-metabolizing enzymes may be more notable for subjects who are at the extremes of metabolic capacity such as the homozygous for defective genes (PMs) or those with duplicated or amplified functional genes (UMs). While PMs may achieve high plasma/serum concentrations of a drug given at a standard dose with possible risk of an exaggerated response, the UMs may not reach optimal levels and this might account for lack of therapeutic effect. The CYP polymorphisms associated with the greatest clinical implications involve CYP2C9, CYP2C19 and CYP2D6. Phenotyping and/or genotyping should allow the identification of patients at risk of inefficacy or toxicity and offer tools to individualize drug prescription.

In recent years, the major CYP isoenzymes have been characterized at the molecular level and their various substrates, inhibitors and inducers have been identified [5 11]. As shown in Table I, the majority of commonly used psychotropic drugs are metabolized by

Table I. Cytochrome P450 isoforms and psychotropic drugs as substrates, inhibitors or inducers. Modified from Spina - de Leon [4].

CYP isoform	Psychotropic drugs		
	Substrates	Inhibitors*	Inducers*
CYP1A2	*Antidepressants*: tricyclics (demethylation), fluvoxamine, trazodone, duloxetine, mirtazapine, agomelatine *Antipsychotics*: haloperidol, thioridazine, clozapine, olanzapine, asenapine	Fluvoxamine (potent)	Carbamazepine
CYP2B6	*Antidepressants*: bupropion		Carbamazepine
CYP2C9	*Antidepressants*: fluoxetine Mood stabilizers: valproic acid *Hypnotics*: zolpidem, zopiclone	Fluoxetine (moderate) Fluvoxamine (moderate) Valproic acid (weak)	Carbamazepine
CYP2C19	*Antidepressants*: tricyclics (demethylation), sertraline, citalopram, escitalopram, moclobemide *Anxiolytics*: diazepam, clobazam	Fluvoxamine (potent) Fluoxetine (moderate)	Carbamazepine
CYP2D6	*Antidepressants*: tricyclics (hydroxylation), fluoxetine, fluvoxamine, paroxetine, citalopram, escitalopram, venlafaxine, mirtazapine, duloxetine, vortioxetine *Antipsychotics*: haloperidol, chlorpromazine, fluphenazine, perphenazine, thioridazine, zuclopenthixol, pimozide, clozapine, olanzapine, risperidone, iloperidone, aripiprazole, brexpiprazole	Fluoxetine (potent) Paroxetine (potent) Sertraline (moderate) Duloxetine (moderate) Bupropion (moderate) Thioridazine (potent) Perphenazine (potent) Asenapine (weak)	
CYP3A4	*Antidepressants*: tricyclics (demethylation), sertraline, citalopram, escitalopram, venlafaxine, mirtazapine, trazodone, reboxetine, vilazodone *Antipsychotics*: haloperidol, thioridazine, pimozide, clozapine, quetiapine, risperidone, iloperidone, aripiprazole, brexpiprazole, ziprasidone, lurasidone, cariprazine *Anxiolytics*: alprazolam, midazolam, triazolam *Mood stabilizers*: carbamazepine	Fluoxetine (moderate) Fluvoxamine (moderate)	Carbamazepine

* Inducers and inhibitors are restricted to psychotropic drugs.

CYP enzymes and some may also act as inhibitors or inducers of one or more of these isoforms, thus resulting in metabolically-based drug interactions [4].

Role of CYP isoforms in the metabolism and clinical response to psychotropic drugs

The most relevant CYP isoforms involved in the metabolism of psychiatric drugs include CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Polymorphism of genes encoding for these enzymes result in different rates of psychotropic drug metabolism potentially increasing the risk for adverse effects or reducing therapeutic response. The currently known evidence of the impact of genetic variants of the major CYP isoforms on the metabolism and pharmacological response to psychotropic medications is described.

CYP1A2

CYP1A2 is an isoform accounting for about 10-15% of total hepatic CYPs [12]. The *CYP1A2* gene has been mapped on to chromosome 15q24.1 [3]. So far, more than 21 variant alleles and a series of subvariants (**1B* to **21*) of the *CYP1A2* gene have been identified [6]. While some variants show decreased activity (**1C*, **1K*, *8, **11, *15* and **16*), the variant **1F is* associated with increased inducibility among smokers [6]. The large interindividual variability in CYP1A2 activity may be partly due to environmental factors such as inhibitors (i.e., ciprofloxacin and fluvoxamine) or inducers (i.e., carbamazepine and cigarette smoking).
CYP1A2 plays a significant role in the metabolism of a variety of clinically important drugs, including theophylline, caffeine, phenacetin, propranolol, tacrine and a number of antidepressants and antipsychotics [12].

Antidepressants

The biotransformation of several antidepressants is partially mediated by CYP1A2. This enzyme has been shown to contribute to the demethylation of TCAs [13]. Together with CYP2D6, CYP1A2 is involved in the metabolism of the selective serotonin reuptake inhibitor (SSRI) fluvoxamine. In this respect, some studies have reported an effect of smoking (an inducer of CYP1A2) on fluvoxamine disposition [14 15]. CYP1A2 is also the main enzyme responsible for the metabolism of the new antidepressant agomelatine [16]. Consistent with this, the use of agomelatine is contraindicated in patients taking fluvoxamine, a potent CYP1A2 inhibitor [16]. In addition, CYP1A2 contributes to the biotransformation of duloxetine [17], mirtazapine [18] and trazodone [19]. To our knowledge, no pharmacogenetic study has so far evaluated the effect of CYP1A2 gene variants on the pharmacokinetics of these antidepressants.

Antipsychotics

CYP1A2 is involved in the biotransformation of the first-generation antipsychotics haloperidol and thioridazine [20]. On the other hand, CYP1A2 plays a major role in the metabolism of the newer antipsychotics clozapine [21], olanzapine [22] and asenapine [20].
The major metabolic pathways of clozapine include the demethylation to norclozapine, mediated by CYP1A2, CYP2C19, and CYP3A4, and the oxidation to clozapine N-oxide, mediated by CYP3A4 [21]. In a study of schizophrenic patients, the CYP1A2 genetic polymorphisms **1F* and **1D* did not affect significantly clozapine clearance [23]. Higher serum concentrations of clozapine and norclozapine have been observed in patients carrying two *CYP1A2* variants associated with reduced enzyme activity (–3860A, –2467del, –163C, –739G, and/or –729T), compared with those with one or none [24].
Olanzapine is primarily metabolized via direct N-glucuronidation, mediated by UGT1A4, and N-demethylation, catalyzed by CYP1A2 [22]. Studies investigating the impact of CYP1A2 on the pharmacokinetics of olanzapine produced conflicting results [25-27]. On the other hand, in a study of schizophrenic patients treated with olanzapine, subjects with the *CYP1A2*1F*/**1F* genotype had 22% lower (dose and bodyweight adjusted) serum olanzapine concentrations compared to *CYP1A2*1A* carriers [28].
The new antipsychotic asenapine is cleared through oxidative metabolism, primarily by CYP1A2, and by direct glucuronidation [20].
Based on the available evidence, routine genotyping for CYP1A2 allelic variants is not yet indicated in psychiatry.

CYP2B6

CYP2B6 represents a relatively small proportion (about 2-6%) of the total hepatic CYPs [6 12]. The *CYP2B6* gene is located at chromosome 19 between 19q12 and 19q13.2 and is highly polymorphic [3]. The variant alleles *CYP2B6*6*, *CYP2B6*16* and *CYP2B6*18* are associated with lower expression/activity, while the allele *CYP2B6*4* appears to be as-

sociated with increased activity. CYP2B6 plays an important role in the metabolism of the anticancer drugs cyclophosphamide and ifosfamide, the anti-HIV agents efavirenz and nevirapine, the anesthetics propofol and ketamine, the antiparkinsonian drug selegiline, the atypical antidepressant and smoking cessation agent bupropion, and the μ-opioid agonist methadone [6]. The activity of CYP2B6 may be affected by inhibitors, such as clopidogrel and ticlopidine, and inducers, including carbamazepine and rifampicin.
According to *in vitro* studies, CYP2B6 is the main enzyme responsible for the metabolism of bupropion [29]. In a study of healthy volunteers, bupropion total clearance was higher in carriers of the allele *CYP2B6*4* compared to carriers of wild-type allele **1* [30]. In a genotype-guided study of 42 healthy subjects, Benowitz et al. [31] found that *CYP2B6*6* and **18* gene variants were associated with approximately 33% reduced concentrations of hydroxybupropion at steady-state, with no effects on concentrations of bupropion or other metabolites.
At present, genotyping for CYP2B6 has no clinical utility in psychiatry.

CYP2C9

CYP2C9 is largely represented in human liver where it corresponds to approximately 20% of the hepatic total CYP content [32]. The *CYP2C9* gene is located at chromosome 10q24 in a densely packed region also containing genes encoding other CYP2C subfamily members such as CYP2C8, CYP2C18 and CYP2C19 [3]. *CYP2C9* exhibits genetic polymorphisms and, to date, more than 35 allelic variants have been described [32]. The two more common variants associated with reduced enzyme activity are *CYP2C9*2* and *CYP2C9*3*. There are significant inter-ethnic differences in the frequency of these two variants [3]. *CYP2C9*2* and *CYP2C9*3* are mainly present in Caucasians at a frequency of 11% and 7% respectively, while frequencies are lower in Africans. *CYP2C9*2* has indeed not been detected in Asians [6].
CYP2C9 is primarily involved in the biotransformation of a variety of therapeutic agents including nonsteroidal anti-inflammatory drugs, oral antidiabetics, diuretics, angiotensin II receptor antagonists, anticancer drugs, oral anticoagulants (e.g., S-warfarin) and antiepileptics (e.g., phenobarbital and phenytoin). On the other hand, CYP2C9 plays only a minor role in the metabolism of a number of psychotropic drugs, namely TCAs, fluoxetine, valproic acid, and the Z-drugs zolpidem and zopiclone [32].
Genotyping for CYP2C9 is not likely to have any clinical use in psychiatry.

CYP2C19

CYP2C19 is expressed at relatively low levels in human liver. The CYP2C19 gene is located on chromosome 10q24.1-q24.3 and is highly polymorphic with at least 35 allelic variants and subvariants *(*1B* to **34*) identified so far [33]. *CYP2C19*1*, the wild-type allele encoding a fully functional enzyme, is present in double or single copy in EMs (homozygotes or heterozygotes, respectively). CYP2C19 PMs are carriers of null alleles *CYP2C19*2* and *CYP2C19*3*. The prevalence of CYP2C19 PMs is about 2 to 5% in Caucasians but up to ~25% in Asians. There is a marked inter-ethnic variation in the distribution of these two variant alleles [33 34]. The allelic frequency of *CYP2C19*2* has been shown to be 15% in Africans, 29-35% in Asians, 12-15% in Caucasians and 61% in Oceanian peoples. *CYP2C19*3* is mainly found in Asians (5-9% in Asians, less than 0.5% in Caucasians). A *CYP2C19* gene variant (*CYP2C19*17*), associated with increased gene transcription and thus a higher metabolism of CYP2C19 substrates has been described [35]. Its frequency varies quite broadly between different ethnic groups, being 18% among Swedes and 4% in Chinese.
CYP2C19 is responsible for the oxidative metabolism of some widely used drugs such as proton pump inhibitors, clopidogrel and various psychotropic medications including some TCAs, SSRIs and benzodiazepines [3 12 36]. Many studies have investigated the relationship between the CYP2C9 genetic polymorphism and the pharmacokinetics of these drugs, but only a few have examined its possible influence on clinical outcomes.

Antidepressants

It is well documented that CYP2C19 is the major enzyme involved in the demethylation of tertiary TCAs amitriptyline, imipramine and clomipramine to secondary amines, but other CYPs, namely CYP2C9, CYP3A4 and CYP1A2, may also contribute [13]. Two studies in depressed Japanese patients reported higher plasma concentrations of imipramine in CYP2C19 PMs as compared to EMs [37 38]. Pharmacokinetic investigations in Japanese [39] and Caucasian psychiatric patients [40 41] found that steady-state serum concentrations of amitriptyline were higher in subjects with two *CYP2C19*-mutated alleles *(*2,*3)* as compared to subjects with wild-type genotype. Dose-

and weight-adjusted steady-state concentrations of clomipramine were 41% and 76% higher in patients with two mutated *CYP2C19* alleles than individuals carrying one defective *CYP2C19* allele or none, respectively [42]. Two studies involving a large sample of depressed patients documented that subjects homozygous for *CYP2C19*17*, the variant associated with higher enzyme activity, had lower plasma concentrations of amitriptyline [43] and imipramine [44] compared with *CYP2C19*1/*1* individuals. Dosing recommendations for TCAs based on CYP2C19 genotyping have been suggested and summarized in Table I [45-47].

With regard to SSRIs, CYP2C19 is the most important isoform responsible for the demethylation of sertraline to an almost inactive metabolite. A single-dose pharmacokinetic study in healthy subjects reported that the area under the curve (AUC) of sertraline was 41% higher in CYP2C19 PMs compared with EMs [48]. Citalopram and escitalopram are metabolized primarily by CYP2C19 and CYP3A4 and, to a lesser extent, by CYP2D6 [49]. A population pharmacokinetic study in Chinese patients reported that the oral clearance of citalopram in CYP2C19 PMs was 43 and 33% lower compared with the homozygous and heterozygous EMs, respectively [50]. In a study involving 166 patients treated with escitalopram, the serum concentrations of escitalopram were 42% lower in patients homozygous for *CYP2C19*17* and 5.7-fold higher in subjects homozygous for defective *CYP2C19* alleles, compared with the *CYP2C19*1/*1* subgroup [51]. Despite this correlation, the influence of CYP2C19 variants on the clinical outcome with sertraline, citalopram and escitalopram is presumably low, due to the large therapeutic window of these antidepressants.

Based on this evidence, the CYP2C19 genetic polymorphism appears to play only a marginal role on the pharmacokinetics and clinical response to newer antidepressants, so the usefulness of CYP2C19 genotyping techniques as a guide for dose individualization is probably limited. Nevertheless, Hicks et al. [52] suggested dosing recommendations for CYP2C19 and SSRIs (Tab. II).

Other psychotropic drugs

CYP2C19 plays a role in the complex metabolism of clozapine. In this respect, higher serum clozapine concentrations have been described in CYP2C19 PM patients than in those with other CYP2C19 geno-

Table II. Pharmacogenetic guidelines using CYP2C19 and CYP2D6 genotyping for dosing psychiatric drugs. Based on refs. [45-47 52 78 79].

Psychotropic drug	Recommendations
TCAs	CYP2D6 PMs: avoid TCAs or ↓ dose by 50% and use TDM to adjust dosing. CYP2D6 UMs: avoid TCAs. CYP2C19 PMs and amitriptyline: ↓ dose by 50% and use TDM to adjust dosing CYP2C19 UMs and amitriptyline: select another antidepressant not metabolized by CYP2C19
Citalopram, escitalopram and sertraline	CYP2C19 PMs: select another antidepressant or ↓ dose by 50% and use TDM to adjust dosing CYP2C19 UMs: select another antidepressant
Fluoxetine, fluvoxamine and paroxetine	CYP2CD6 PMs: select another antidepressant or ↓ dose by 50% and use TDM to adjust dosing (Hicks et al. 2015) CYP2C19 UMs: select another antidepressant
Venlafaxine	CYP2D6 PMs: select another antidepressant or use venlafaxine TDM CYP2D6 UMs: increase dose by a factor of 1.5
Aripiprazole, haloperidol, risperidone and zuclopenthixol	CYP2D6 PMs: ↓ dose by 50% or select another antipsychotic CYP2D6 UMs: be alert to diminished serum concentrations or prescribe another antipsychotic.
Long-acting intramuscular aripiprazole	CYP2D6 PMs: ↓ dose to 75%*
Pimozide	If prescribing > 4 mg/day in adults, CYP2D6 genotyping is required by the US prescribing information because 4 mg/day is the maximum recommended dose in CYP2D6 PMs.

* Inducers and inhibitors are restricted to psychotropic drugs.

types [53]. Further studies are needed to evaluate the impact of CYP2C19 genetic polymorphism on clozapine disposition.
Some benzodiazepines, including diazepam and clobazam, are extensively metabolized by CYP2C19, with partial contribution from CYP2C18, CYP3A4, and CYP2B6 [54].

CYP2D6

CYP2D6 is the most important polymorphic enzyme involved in drug metabolism but accounts for less than 5% of the hepatic total CYP content [12]. The gene encoding for CYP2D6 is located in position 22q13.1 and is highly polymorphic. Currently more than 100 allelic variants and subvariants have been identified, and there are substantial interethnic differences in allele frequencies [55]. While some variants encode an inactive enzyme or no enzyme at all, others consist of gene duplication. Therefore, CYP2D6 activity may range from complete deficiency to ultrarapid metabolism and individuals are classified as PMs, IMs, EMs or UMs according to their inherited genetic profile. PMs lack CYP2D6 activity and represent approximately 3 to 10% of Caucasians, but only 1 to 2% of East Asians. Among EMs, the catalytic activity varies largely, and a subgroup of subjects with extremely high enzyme activity has been classified as UMs. Four major mutated alleles, *CYP2D6*3*, *CYP2D6*4*, *CYP2D6*5* and *CYP2D6*6*, account for 90-95% of the PM alleles in Caucasians. Alleles with duplication or multiduplication of a functional *CYP2D6*2* gene are associated with increased CYP2D6 activity: the frequency of this condition varies from 1-2% in Swedes to up to 7-10% in Spaniards and Southern Italians. Most of the CYP2D6 UMs probably have 3 active copies but as many as 13 copies have been described. A comprehensive worldwide study provided CYP2D6 UM frequencies of 1-5% in Caucasians, 40% in northern Africa and > 20% in Oceania [56].
Differently from other CYPs, CYP2D6 is not inducible, and thus genetic mutations are largely responsible for the interindividual variation in enzyme expression and activity. On the other hand, the activity of CYP2D6 can be inhibited by several drugs including quinidine, perphenazine, thioridazine, fluoxetine and paroxetine, resulting in clinically significant drug interactions [5].
CYP2D6 plays an important role in drug metabolism, being partially or entirely responsible for the oxidative biotransformation of commonly prescribed drugs such as antidepressants, antipsychotics, opioids, antiemetics, antiarrhythmics, beta-blockers, tamoxifen and atomoxetine [55 57].

Antidepressants

Most antidepressants including TCAs, SSRIs and other newer agents are metabolized, at least in part, by CYP2D6 [57].
TCAs are first-generation agents with a relatively narrow therapeutic index. Clinical effects of TCAs appear to be correlated with their serum concentrations [58]. TCAs include tertiary amines (amitriptyline, imipramine, clomipramine) and secondary amines (nortriptyline, desipramine). Tertiary amines are demethylated to secondary amines, while both tertiary and secondary are further hydroxylated to active metabolites. It is well documented that the hydroxylation reactions of TCAs are catalyzed by CYP2D6, whereas N-demethylation is catalyzed by CYP2C19 and, to a lesser extent, by CYP1A2, CYP2C9 and CYP3A4 [13].
The best correlation between CYP2D6 genotype and pharmacokinetics and steady-state serum concentrations has been observed for the secondary amines nortriptyline and desipramine. On the other hand, the impact of CYP2D6 genotype on the elimination kinetics of tertiary amines is lower presumably due to the involvement of multiple CYP isoforms in their biotransformation. Several investigations in healthy subjects found significant differences in the pharmacokinetic parameters of TCAs between CYP2D6 PMs and EMs [13 57]. In general, CYP2D6 PMs reach higher peak serum concentrations, and have lower clearances and longer half-lives as compared with CYP2D6 EMs. Interestingly, Dalen et al. [59] showed that the number of active *CYP2D6* gene copies had a strong impact on the pharmacokinetics of nortriptyline in healthy subjects. Earlier pharmacokinetic studies in depressed patients had documented a significant correlation between CYP2D6 activity and steady-state serum concentrations of imipramine [60], nortriptyline [61] or desipramine [62]. The relevance of CYP2D6 variants on clinical outcomes in patients treated with TCAs is documented by several ADR cases with increased serum TCA concentrations in CYP2D6 PMs or therapeutic failure associated with decreased concentrations in CYP2D6 UMs [13].
SSRIs are currently the most widely used antidepressant drugs. Different from TCAs, SSRIs have a wide therapeutic index and no evident correlation between serum levels and clinical outcome has been demonstrated [63]. Therefore, genetically dependent interindividual differences in their elimination have probably a limited clinical relevance. CYP2D6 plays a major

role in the biotransormation of fluoxetine and paroxetine, and contributes to that of fluvoxamine and citalopram/escitalopram [63]. Fluoxetine is N-demethylated to the active metabolite norfluoxetine primarily by CYP2D6 and, to a lesser extent, by CYP2C9, CYP2C19 and CYP3A4 [49]. Some studies in depressed patients treated with fluoxetine reported significantly lower steady-state serum concentrations of fluoxetine (and norfluoxetine) in CYP2D6 EMs than in PMs [64 65], whereas other reported an effect of genotype only on S-enantiomer metabolism [66 67]. Paroxetine is extensively metabolized in the liver by CYP2D6 with additional contribution of CYP3A4 [49]. A number of pharmacokinetic investigations in depressed patients have documented an association between CYP2D6 genotype and steady-state serum concentrations of paroxetine [64 68 69]. CYP2D6 and CYP1A2 are the major CYP isoforms involved in the metabolism of fluvoxamine. Studies evaluating the possible correlation between CYP2D6 genetic polymorphisms and pharmacokinetic parameters of fluvoxamine produced conflicting results suggesting that the contribution of CYP2D6 to the overall clearance of fluvoxamine is probably marginal [70 71]. As previously mentioned, CYP2D6 plays only a minor role in the biotransformation of citalopram and escitalopram [49 63].

Polymorphic CYP2D6 is also involved in the metabolism of antidepressants of the SNRI class. The demethylation of venlafaxine to the active metabolite O-desmethylvenlafaxine is primarily mediated by CYP2D6 [72 73]. In theory, as venlafaxine and its metabolite have similar pharmacological properties, the clinical implications of polymorphic venlafaxine metabolism should not be particularly relevant. However, symptoms of cardiotoxicity (palpitation, shortness of breath, arrhythmia) were reported in four CYP2D6 PM patients while treated with venlafaxine [74]. The SNRI duloxetine is extensively metabolized in the liver primarily by CYP1A2 and, to a lesser extent, by CYP2D6 [17]. Different CYPs including CYP2D6, CYP1A2 and CYP3A4 mediate the biotransformation of mirtazapine, a noradrenergic and specific serotonergic antidepressant (NaSSA) [18]. The multimodal antidepressant vortioxetine is extensively metabolized in the liver by CYP2D6 with additional participation of several CYP isoforms [75]. As PMs achieve twice the plasma concentrations of EMs, they should receive a maximum vortioxetine dosage of 10 mg/day [75].

In conclusion, several lines of evidence indicate that most antidepressants are metabolized, at least in part, by the polymorphic CYP2D6. This explains the significant interindividual variability in serum concentrations of these agents and the interactions observed when these drugs are used in combination with other substrates or inhibitors of the enzyme. The clinical significance of this association is most pronounced for TCAs, since have a narrow therapeutic index and their effects are concentration-dependent. Patients with a decreased ability to eliminate these drugs, either because of a genetic or environmentally-induced deficiency in CYP2D6, are at risk of developing severe adverse effects with conventional doses. Conversely, UMs with duplicated or multiduplicated CYP2D6 genes could require higher than normal doses for optimal treatment. A number of studies have shown a higher incidence of UMs among non-responders to antidepressants primarily metabolized by CYP2D6, in particular TCAs and SSRIs [76 77]. As a result, genotyping for CYP2D6 may be used to supplement the measurement of serum TCA concentrations when aberrant metabolic capacity (poor or ultrarapid) is suspected. On the other hand, the impact of CYP2D6 polymorphisms on clinical outcome in patients treated with newer antidepressants remains to be seen. Specific CYP2D6 genotype-based dose recommendations for a number of antidepressants have been recently developed and described in Table II [45-47 52 78 79].

Antipsychotics

Polymorphic CYP2D6 is responsible for the oxidative metabolism of various first- and second-generation antipsychotics [20 57 80 81].

Concerning first-generation compounds, studies in both patients and healthy volunteers have demonstrated that CYP2D6 is the major enzyme involved in the biotransformation of perphenazine [82 83] and zuclopenthixol [82]. The metabolism of haloperidol and thioridazine is mediated by both CYP2D6 and CYP3A4 [84 85]. Interestingly, patients with CYP2D6 PM phenotype have been reported to reach higher serum concentrations of haloperidol than EMs [86-88]. A study involving 76 psychiatric patients documented that dose-corrected serum thioridazine concentrations were 1.8- and 3.8-fold higher ($p < 0.01$ for both) in subjects with one or no active CYP2D6 alleles, respectively, compared with those with two or more functional alleles [88]. CYP2D6 plays a major role in the metabolism of pimozide and PMs reach higher serum concentrations than EMs. As the occurrence of pimozide-induced arrhythmias is concentration dependent, the US prescribing information recommends CYP2D6 genotyping for prescribing pimozide doses > 4 mg/day [90] (Tab. II).

The second-generation antipsychotic risperidone is converted by CYP2D6 and, to a lesser extent, by CYP3A4 to the active metabolite 9-hydroxyrisperidone or paliperidone, which has a similar potency compared with the parent drug in terms of dopamine receptor affinity. Pharmacokinetic studies in patients treated with risperidone found that the ratio of risperidone to 9-hydroxyrisperidone concentrations at steady-state is strongly associated with the *CYP2D6* genotype, with the highest ratios in PMs and the lowest in UMs; nevertheless the sum of the active moieties was substantially comparable among the various genotype groups [91 92]. It may be assumed that CYP2D6 genetic polymorphism have no relevant clinical implications for risperidone metabolism as decreased 9-hydroxyrisperidone production would be compensated for by higher serum levels of the parent drug, risperidone. However, a number of studies described a higher incidence of ADRs, including lengthening of QTc interval and parkinsonism, in CYP2D6 PM patients, presumably reflecting pharmacological differences between parent drug and metabolite [93-96]. Aripiprazole is metabolized by CYP2D6 and CYP3A4 to dehydroaripiprazole, an active metabolite with pharmacological properties similar to the parent drug. Aripiprazole is the major moiety in systemic circulation, while dehydroaripiprazole represents roughly 40% of aripiprazole exposure. Patients with the CYP2D6 PM phenotype have an 80% increase in aripiprazole blood levels and a 30% decrease in dehydroaripiprazole levels, resulting in a 60% higher exposure to the total active moieties; the elimination half-life of aripiprazole and dehydroaripiprazole was found to increase significantly in PMs [20]. Based on the US and EU prescribing information, long-acting aripiprazole should be administered at monthly doses of 400 mg in average individuals [97]. However, this dose should be reduced to 300 mg in CYP2D6 PMs and 200 mg in CYP2D6 PMs taking CYP3A4 inhibitors. On the other hand, CYP2D6 plays only a minor role in the metabolism of clozapine and olanzapine. Accordingly, a number of studies found no differences in steady-state serum concentrations of both antipsychotics in the various phenotype groups [23 24 27 98 99].

Many studies have investigated the relationship between CYP2D6 polymorphisms, steady-state serum concentrations, and therapeutic and adverse effects of various antipsychotic drugs [20 81]. Results may be considered controversial partly due to differences in methodology (e.g., retrospective and prospective open-label studies as well as case-control studies), small sample size and heterogeneity of studied populations. Grossman et al. [100] examined the influence of 25 genetic variants of drug metabolizing enzymes in a subgroup of patients (n = 750) who were enrolled in the large CATIE study; these patients were treated with olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine. None of the variants investigated (including CYP2D6) showed a significant association with dosing, efficacy or overall tolerability.

In conclusion, there is a significant body evidence suggesting a relationship between CYP2D6 genetic polymorphisms and the pharmacokinetic parameters of many antipsychotics such as perphenazine, haloperidol, pimozide, risperidone and aripiprazole. On the other hand, findings on the association between polymorphic CYP2D6 and response to these antipsychotics are not in agreement. Therefore, recommendations for antipsychotics dose adjustments based on CYP2D6 are not likely to be made in the near future, although published recommendations exist for some antipsychotics (Tab. II).

CYP3A4

CYP3A4 is the most abundant CYP isoform, accounting for about 30% of total CYP in the human liver and 70% in the small intestine [3]. The gene encoding for CYP3A4 is located on chromosome 7q21-q22.1 along with the other members of the CYP3A sub-family (CYP3A4, CYP3A5, CYP3A7 and CYP3A43). Several polymorphisms of CYP3A4 have been identified, but most are extremely rare and occur as heterozygotes with the wild-type allele, while others have no demonstrable effect on substrate metabolism [12]. Only the variants CYP3A4*6, CYP3A4*17, CYP3A4*20 and CYP3A4*22 display functional variability with decreased activity, whereas CYP3A4*18A is associated with increased activity [3]. The activity of CYP3A4 may be increased by potent inducers such as rifampin and antiepileptic inducers. A number of drugs including ketoconazole, itraconazole, erythromycin and troleandomycin, act as potent CYP3A4 inhibitors. Grapefruit juice is also a known inhibitor of CYP3A4.

CYP3A4 is involved in the biotransformation of over 50% of therapeutic agents. Drugs primarily metabolized by CYP3A4 include immunosuppressants (e.g., cyclosporin and tacrolimus), non-sedating antihistamines (e.g., terfenadine and astemizole), calcium antagonists (e.g., diltiazem, verapamil, nifedipine and other dihydropyridines), cholesterol lowering drugs (e.g., simvastatin and lovastatin), antiarrhythmics (e.g., amiodarone and quinidine), and several steroids (e.g., cortisol, ethinylestradiol and levonorgestrel) [12].

CYP3A4 plays an important role also in psychopharmacotherapy as it contributes to the biotransformation of various antidepressants (TCAs, sertraline, citalopram, escitalopram, venlafaxine, mirtazapine and reboxetine), antipsychotics (haloperidol, pimozide, clozapine, quetiapine, risperidone, aripiprazole, ziprasidone, lurasidone and brexpiprazole), mood stabilizers (carbamazepine) and benzodiazepines (e.g., alprazolam, midazolam and triazolam).

CYP3A4 is primary involved the metabolism of the newer antipsychotics quetiapine and lurasidone. To date, there is limited evidence of an association between these variants and antipsychotic response. A recent study in 238 patients treated with quetiapine found that dose-corrected serum concentrations of quetiapine were 67% higher ($p = 0.01$) in carriers of the CYP3A4*22 allele (*1/*22 and *22/*22, $n = 31$) than in wild-type patients ($n = 207$) [101].

CYP3A4 is the major enzyme responsible for the epoxidation of carbamazepine, an antiepileptic agent also used as a mood stabilizer. In study involving 90 patients with epilepsy patients, the *CYP3A4*1B* was associated with lower carbamazepine clearance [102]. There is no known clinical use for genotyping for CYP3A4 in psychiatry.

Clinical usefulness of CYP genotyping procedures in psychiatry

Pharmacological treatment can be personalized by basing drug selection and dose on the needs of the individual [1]. CYP genotyping is one factor on which such personalized medicine can be based. CYP genotyping is currently performed only when issues relating to efficacy, such as non-response, or safety, such as ADRs or abnormal TDM, arise. However, advances in genotyping technology and the increasing affordability of associated costs are making it more likely that CYP genotyping is carried out even before psychiatric medication is prescribed [103].

Some CYPs, namely CYP1A2, CYP2B6, CYP2C9 and CYP3A4, may be of interest for research in psychiatry, but are of limited clinical use for many reasons:

1) there is little scientific evidence regarding these CYPs, and such evidence is rarely replicated, and therefore validated;
2) it is not clear what the relationship between phenotype and genotype may be;
3) the impact of genetic variations in these CYPs is not likely to be more significant than environmental factors.

On the other hand, genotyping for CYP2D6 and CYP2C19 may be useful in psychiatry in certain clinical situations. A summary of the pharmacogenetic guidance for CYP2C19 and CYP2D6 as well as associated dosing regimens of selected psychiatric drugs is found in Table II [46 47 52].

Psychiatric medication such as antidepressants are prescribed not only by psychiatrists but also by general practitioners. However, prescribers require training in order to have the expertise needed to make use of genotyping to improve efficacy and safety outcomes. This is particularly true when prescribing TCAs and when treating rare subjects who are PMs for both CYP2C19 and CYP2D6 (< 1/1000). Such persons lack both CYPs and are expected to be unable to metabolize TCAs as well as the newer antidepressants [104].

Clinicians need to be familiar with current genotyping methods and the next generation of sequencing technologies. Samer et al. [105] describe currently applied methods available for the most common CYP genotyping required by psychiatrists, that is, of CYP2D6 and CYP2C19. The AmpliChip CYP450 GeneChip is the best-studied tool used to carry out such genotyping [79 106].

One obstacle to the use of genotyping is the large variety of genotyping methods and outputs for CYP2D6 and CYP2C19 provided by clinical laboratories. It may be advisable for prescribers to use the services of one laboratory and familiarize themselves with the strengths and limitations of the methods used for genotyping. Even though CYP2D6 and CYP2C19 genotype-phenotype relationships are relatively well-known, the existence of rare new alleles is still coming to light. As a matter of fact, a recent review [107] indicates that the vast majority of genetic variations at the CYP genes may be very rare. It is not clear how much these rare variations can impact clinical practice but combining CYP genotyping and therapeutic drug monitoring (TDM) may be the current answer to this uncertainty. In summary in our opinion, to correctly interpret CYP2D6 or CYP2C19 genotyping, prescribers require a complete drug history and ideally also TDM results.

Novel sequencing technologies have permitted the description of variations in the human genome in ways that were not possible until recently, and this has helped understand the role of rare variations in drug response [108]. Nevertheless, CYPs are not idea for novel sequencing methods due to their genomic complexity [109]. In addition, rare CYP variants may be particularly significance in African populations where

there is notable discordance between CYP genotypes and phenotypes [110].

As genetic technology rapidly advances, the cost of genetic testing in general, and of CYP genotyping in particular, is drastically falling. A recent review in pharmacogenomics found two types of cost studies (cost-effectiveness studies and cost-utility studies) but no corresponding published study in psychiatry [111]. It was easier to probe the cost-effectiveness of CYP testing in psychiatry when the old antipsychotics and antidepressants were the main drugs prescribed in psychiatry, because these drugs have a narrow therapeutic window and are highly dependent on CYP2D6 and CYP2C19 for their metabolism [112]. The newer psychiatric drugs have wider therapeutic windows and more varied metabolic pathways, making it difficult to complete cost studies in CYP genotyping. Therefore, large prospective studies aiming to deliver "proof of concept" outputs as well as describe the cost-benefit ratio CYP genotyping in psychiatry are unlikely to be conducted, as these are very expensive.

In order to personalize drug dosing, prescribers should take into consideration also environmental (inhibitors and inducers) and personal (e.g., age, gender, illnesses) factors, in addition to genetic ones [1]. This global vision of patient health requires TDM, as this reflects the influence of environmental and personal factors involved in metabolism, as well as the transport of drugs and the measurement of active metabolites [103]. The combination of CYP genotyping and TDM may find its way into clinical practice in the near future in order to improve the safety and efficacy of some psychiatric drugs [103]. In this respect, a group of European psychiatrists has published the most comprehensive TDM guidelines in psychiatry [58].

To be clinically useful in the future, pharmacogenetic testing may need to include epigenetic factors, pharmacokinetics and pharmacodynamics, therapeutic windows, idiosyncratic and dose-related ADRs, and should be used in association with TDM and other phenotyping tests [103].

The lack of agreement on regulatory issues by agencies in charge in USA and some European countries has left a vacuum for companies to take advantage of by marketing non-validated pharmacogenetic tests with no, or very limited, data on clinical validity and utility [113]. We propose that genetic testing for 1) CYP1A2, CYP2B6, CYP3A4 or CYP3A5; 2) brain neurotransmitters and/or transporter genes; and 3) diagnosing schizophrenia, depression or bipolar disorder should not be ordered by clinicians since there is no data supporting their clinical validity and utility [114].

Conclusions

This article has summarized the current evidence regarding the role of CYP genetic variants in pharmacokinetics and clinical response to the most commonly used psychotropic drugs. The implications of CYP genotyping techniques in psychiatry have been critically reviewed. As there have been limited validated findings from well-controlled studies that could orient clinicians in the use of CYP genotyping in clinical work, the present paper is focused on the available evidence-based medicine data, interpreting this in a clinical light.

CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 genetic polymorphisms and their contributions to the metabolism of psychotropic drugs were thoroughly reviewed. CYP1A2, CYP2B6 and CYP3A4 genotyping may be of interest in an academic context, but have limited clinical usefulness at present. CYP2C9 can be used for clinical testing but does not currently have a place in psychiatry. CYP2D6 and CY2C19 genotyping are the most important kinds of CYP genotyping for psychiatrists. Recommendations from practice guidelines describing CYP2D6 and CY2C19 genotyping for dosing several psychiatric drugs were reviewed in detail (Tab. II).

TCAs have a narrow therapeutic window and pose substantial risk of ADRs, including potentially fatal dose-related arrhythmias. Therefore, ADRs are much more likely to occur in CYP2D6 and CYP2C19 PMs, but may be more likely for severe cases of major depression. As a result, expertise in TCA-related genotyping and TDM may be a "niche" skill that psychiatrists need to master in order to dose TCA safely. Practice guidelines recommend prescribing an antidepressant other than venlafaxine or using TDM in CYP2D6 PMs, as well as increasing doses by a factor of 1.5 in CYP2D6 UMs [46]. Practice guidelines also recommend TDM and increasing doses by a factor of 1.5 in CYP2C19 UM patients receiving citalopram or escitalopram; the dose should be halved in CYP2C19 PMs taking sertraline [46]. Individuals who do not have CYP2C19 or CYP2D6 (PMs for both isoenzymes) will have problems metabolizing TCAs and most, but not all, of the newer antidepressants.

The dose of aripiprazole, haloperidol, risperidone, or zuclopenthixol should be reduced by 50% in PMs or an alternative drug used. In UMs on the other hand, clinicians should use TDM or prescribe an alternative drug [46]. The respective long-acting aripiprazole dose in CYP2D6 PMs and CYP2D6 PMs taking CYP3A4 inhibitors should be 75 and 50% of the average

dose [97]. The US prescribing information recommends CYP2D6 genotyping for prescribing pimozide doses > 4 mg/day since CYP2D6 PMs should not take doses > 4 mg/day [90] (Tab. II).

When the evidence is limited, there is need to use the available pharmacological mechanistic information to personalize treatment in psychiatry, for example by combining CYP genotyping with TDM [103].

Conflict of interest

In the past few years, Dr. Spina has participated in speakers/advisory boards and lectures supported by Arcapharma, AstraZeneca, Bristol-Myers, Eli Lilly & Co, Janssen Pharmaceuticals, Lundbeck and Pfizer. He is not a shareholder in any pharmaceutical company.

Dr. de Leon personally develops his presentations for lecturing, has never lectured using any pharmaceutical or pharmacogenetic company presentations, and has never been a consultant for pharmacogenetic or pharmaceutical companies. In the past, Dr. de Leon received researcher-initiated grants from Eli Lilly (one ended in 2003 and the other, as co-investigator, ended in 2007); from Roche Molecular Systems, Inc. (ended in 2007); and, in a collaboration with Genomas, Inc., from the NIH Small Business Innovation Research program (ended in 2010). He has been on the advisory boards of Bristol-Myers Squibb (2003/04) and AstraZeneca (2003). Roche Molecular Systems supported one of his educational presentations, which was published in a peer-reviewed journal (2005). His lectures were supported once by Sandoz (1997), twice by Lundbeck (1999 and 1999), twice by Pfizer (2001 and 2001), three times by Eli Lilly (2003, 2006, and 2006), twice by Janssen (2000 and 2006), once by Bristol-Myers Squibb (2006), and seven times by Roche Molecular Systems, Inc. (once in 2005 and six times in 2006).

Take home messages for psychiatric care

- Genetic polymorphisms of cytochrome P450 (CYP) enzymes play an important role in the pharmacokinetics of many drugs used in psychiatry, in particular antidepressants and antipsychotics
- The influence of CYP variants on pharmacokinetic parameters of psychotropic drugs has not been associated so far with consistent results on a clinical level, that is, in terms of therapeutic effect and adverse events
- Genotyping for allelic variants of CYP2D6 and CYP2C19 can be used to personalize dosing for some antidepressants (i.e., tricyclic antidepressants and venlafaxine) and antipsychotics (i.e., aripiprazole) in certain clinical situations such as non-response or severe adverse effects, but not on a routine basis
- Knowledge of CYP2D6 and CYP2C19 genotype should be integrated with therapeutic drug monitoring, so thus allowing identification of individuals with extreme rates of drug metabolism including poor or ultrarapid metabolizers
- At present, genotyping for CYP1A2, CYP2B6, CYP2C9 and CYP3A4 may be of interest only on a scientific level, but has no clinical utility in psychiatry

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THE ROLE OF RESILIENCE AND COPING STRATEGIES IN DIFFERENT PSYCHIATRIC DISEASES: A COMPARISON AMONG SCHIZOPHRENIC SPECTRUM, DEPRESSION AND PERSONALITY DISORDERS

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Abstract

Objectives: To better understand the relationship between resilience, coping skills and clinical features in diseases like depression, personality disorders and psychosis in a psychiatry ward for acute patients.

Materials: We conducted a cohort prospective study involving 87 out of 338 inpatients admitted in our psychiatry ward, from 1st June 2015 to 31st March 2016. Patients were recruited if they had one of the following diagnoses: schizophrenia spectrum and other psychotic disorder (n = 25); depressive disorder (n = 27), and personality disorder (n = 35). Socio-demographic factors, clinical features, comorbidity and medications of the sample were gathered. Patients' assessment included the following: Resilience Scale for Adult (RSA), Clinical Global Impression scale (CGI) and an abbreviated version of the COPE Inventory (Brief-COPE). Statistical analysis was performed with SPSS. Significance was set for $p < 0.05$.

Results: In patients with schizophrenia spectrum disorders we found a direct correlation between years of illness and the Brief Cope sub-scale "use of emotional support", and an indirect correlation between years of illness and the Brief Cope "divert attention" sub-scale. Patients with a diagnosis of depression, we found an inverse correlation between years of illness and the Brief Cope subscale "positive restructuring".

Conclusions: It is likely that different levels of resilience and coping are evident in a chronic context and are important in the prevention of acute phases of psychiatric disorders. The RSA and Brief Cope differences we found seem to suggest that resilience is more prone to vary in disorders like depression and schizophrenia spectrum disorders, rather than in personality disorders.

Key words: resilience, schizophrenia, depression, personality disorders

Introduction

Resilience is a topic of interest in several disciplines and in the psychiatric field it is defined as the ability to recover from perceived adverse or changing situations, through a dynamic process of adaptation. This process is influenced by personal characteristics, family and social resources, and is expressed by positive coping, control and integration skills [1].

Some researchers have approached resilience as an individual construct [2], while others as an epiphenomenon of an adaptive temperament [3]. In some studies coping skills [4], intended as lasting personal resources,

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which are considered a constitutive element of resilience, would have the function of protecting the individual against a wide range of future adversity.
Other studies have suggested that resilience could be seen as synonymous with reduced vulnerability [5], or as the ability to adapt to adversity [6] or also as the ability to develop strategies for "coping" [7].
In recent years the research in mental health focused on the impact of resilience and coping skills on the patients' actual level of functioning and clinical outcomes [8]. Today it is well known that resilience has an inverse relation with depression [4] and preventative treatment approaches may be focused on it. Furthermore, low levels of resilience are related to an increased number of depressive episodes in euthymic patients with Bipolar Disorder (BD) [9]. Many resilience factors, such as emotional-focused coping skills, internal locus of control, family cohesion and social support, are positively associated with better outcomes in treatment for PTSD, obsessive-compulsive disorder and other Post-Traumatic Stress Disorder [10 11]. For patients affected by schizophrenia spectrum disorders, high resilience levels are linked with less severe positive symptoms, general psychopathological symptoms, depression, and hopelessness. Improvement in social skills and occupational functioning are well-known recovery factors in these patients [12]. High levels of resilience, positive achievement experiences and positive interpersonal relationships during childhood or adolescence were significantly associated with remission for many personality disorders [13]. However, the specific role of resilience in disorders like depression, personality disorders and psychosis is not fully understood; as suggested by the literature it may contribute to the determinism of illnesses' onset, duration, severity, frequency of the relapses, treatment compliance and effectiveness [14]. Furthermore, the literature about the assessment of patient's resilience in acute psychiatric care is still scant, and its implications for treatment in this setting should be better understood.

Objective

The aim of this study is to assess the relationship between resilience, coping skills and clinical features in patients admitted to the psychiatric ward of the "Maggiore della Carità" General Hospital in Novara (Italy), subdivided according to diagnosis in the 3 groups: patients with schizophrenia spectrum and other psychotic disorders, patients with depressive disorders and patients with personality disorders.

Materials e methods

We conducted a retrospective cohort study. We recruited inpatients admitted in our psychiatric ward from the 1st June 2015 to the 31st March 2016. Inclusion criteria were:

- diagnosis of schizophrenia spectrum and other psychotic disorders, depressive disorders and personality disorders according to DSM-IV-TR diagnostic criteria;
- age > 18-years;
- proper understanding of Italian language;
- willingness to give written informed consent.

Patients with mental retardation, dementia or acute drugs intoxication were excluded from the study.
The 3 groups of patients included: 25 patients with schizophrenia spectrum and other psychotic disorders; 27 patients with depressive disorders; 35 patients with personality disorders.
Socio-demographic factors, clinical features, comorbidity and medications of the sample were gathered from clinical charts. Patients' assessment included the following:

- The Resilience Scale for Adults (RSA): a self-report questionnaire consisting of 33 5-point-Likert-scale items. The purpose of this measure is to examine five intrapersonal and extrapersonal prospective factor presumed to facilitate psychosocial adaptation: personal strength, social competence, structural style, family cohesion, social resources [15].
- The Brief-COPE scale (Brief-COPE): This scale assesses a broad scope of coping behaviour among adults. The scale is rated by a 4-point Likert scale and comprises 28 items and 14 dimensions: self distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioural disengagement, venting, positive reframing, planning, humour, acceptance, religion and self-blame [16].
- Clinical Global Impression scale (CGI): a commonly used measure of symptoms severity, treatment efficacy and treatment responses in patients with mental disorders. It consists in 3-item observer-rated measurement: illness severity, global improvement and therapeutic response [17].

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corporation). Categorical variables were ana-

Table I. Social-demographic and clinical features of the sample.

Diagnosis		Depression	Personality Disorder	Schizophrenia spectrum	p value
Characteristic of the sample					
Mean age (year)		51.63	40.7	44.3	0.01
Patients with children		70.40%	42.90%	28.00%	0.004
Family history of psychiatric illness		14.80%	5.70%	60.00%	< 0.010
Occupational status	Unemployed	29.60%	34.30%	28.00%	0.002
	Worker	29.70%	45.70%	32.00%	
	Student	11.10%	8.60%	12.00%	
	Invalid	0.00%	2.90%	28.00%	
	Retired	29.60%	5.70%	0.00%	
	Domestic worker	0.00%	2.90%	0.00%	
Duration of illness (years)		7.5	5.9	12.4	< 0.010
Self-injury acts		92.60%	77.10%	44.00%	< 0.010
Harmful acts		7.40%	40.00%	32.00%	0.009

lyzed with the χ-square test, while continuous variables were analysed with parametric and nonparametric statistics and post-hoc (Tukey). Significance was set for $p < 0.05$.

Results

Patients' main socio-demographic and clinical features are summarized in Table I.

The level of resilience did not differ in the three patients groups. No significant statistical correlation was found among resilience degree and socio-demographic features including: gender, working situation, educational level, presence/absence of psychiatric or physical co-morbidities. Pearson correlations highlighted an inverse correlation between years of illness and the Brief Cope subscale "positive restructuring" ($p < 0.05$) in patients with depression. Furthermore, in schizophrenic patients, we found an inverse correlation between years of illness and the score of the Brief-COPE "divert attention" subscale ($p < 0.05$) in patients with the schizophrenia spectrum disorder. A direct correlation was found between years of illness and the score on the subscale "use of emotional support" of the Brief-COPE ($p < 0.05$) in patients with the schizophrenia spectrum disease. We found that a family history of psychiatric illness is far more frequent in patients affected by schizophrenia spectrum disorders (60%) than in those affected by depressive (14.8%) and personality disorders (5.7%) ($p < 0.05$).

Discussion and conclusion

We suggest some hypotheses to explain these results, which are partially in conflict with the literature data describing a relationship between resilience, coping skills and personality traits [18]. First of all, patients were tested during hospitalization (a stressful event); also, they were observed only for a short period. Probably the different levels of resilience are evident in a chronic context and are important in the prevention of acute stages of disease. In fact, the inverse correlation between positive restructuring and duration of illness in depressed patients suggests that emotional and cognitive coping strategies are likely influenced by the chronicity of this mental illness. Also the correlation between divert attention and years of illness in schizophrenic patients can be explained in the same way. For these patients, the psychopharmacological and psychotherapeutic therapies should begin as soon as possible to avoid the complications due to exacerbation and chronicity of the disorders.

In addition, the significant differences in the RSA and Brief-COPE described before, show that resilience is more likely to vary in diseases such as depression and schizophrenia spectrum disorder than in personality disorders. This can be explained by the intrinsic differences between these diseases; personality disorders seems to be more deeply linked to the nature of the patient structure instead the other two, that have a more fluctuating course.

Take home messages for psychiatric care

- The assessment of patients' resilience and coping skills is fundamental: different levels of resilience are evident in a chronic context and are important in the prevention of acute phases of psychiatric disorders
- The significant differences in the Resilience Scale for Adults (RSA) and Brief-COPE we found show that resilience is more likely to vary in disorders such as depression and schizophrenia spectrum disorder rather than in personality disorders
- Emotional and cognitive coping strategies are influenced by the chronicity of Depressive disorders and Schizophrenia spectrum disorders

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PHARMACOGENETIC AND PHARMACOLOGICAL TREATMENT IN PSYCHIATRIC PATIENTS

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Abstract

Brief introduction: Psychiatric medications metabolized by cytochrome 2D6, may lead to different clinical response, according to patient genetic profiles. Literature's data show that caucasian population is divided in 7% as poor metabolizer, 36% intermediate metabolizer, 50% extensive and 7% ultrarapid metabolizer [1]. The aim of the study is to understand the effects of different metabolic genotype in terms of clinical effectiveness.

Materials and methods: We enrolled 80 psychiatric patients, 38 males and 42 females, mean age at baseline time 43.7 years (range 17-78 years) with a diagnosis of panic disorder (16), mood disorders (36), mood disorders in comorbidity with panic disorders (21) or psychotic disorders (7). All patients were assessed with psychiatric evaluation and treated with psychopharmacological therapy (mood stabilizers, antipsychotics, antidepressants). They were subjected to a genotype analysis in order to evaluate the frequency of the allelic polymorphism of CYP2D6. The genotyping was performed through a DNA amplification technique (PCR) and a microarray technology INFINTY BioFilmChip.

Conclusions: The metabolic genotype of cytochrome 2D6 is directly linked to pharmacotherapy's effectiveness. Poor metabolizers (5% of our sample) showed only side effects and no benefits of the pharmacological treatment. Intermediate metabolizers were 31%; they more likely can develop adverse reactions to polypharmacotherapy and show an incomplete clinical response. Pharmacotherapy shows the best effectiveness in extensive metabolizers (59% in our population). Ultra rapid metabolizers (5% of our sample) had an insufficient clinical response. Testing metabolic genotype of 2D6 in clinical practice could allow us to avoid the onset of side effects and the risk of toxicity as well as recurrent dose corrections and therapy's failure. Moreover, patient's genotyping could help us to customize therapies in terms of doses and times on the basis of patient's genetic profile. Future, larger studies including also pharmacokinetics interactions, patient's compliance and race's genetic differences are warranted to better customize pharmacological therapies.

Key words: cytochrome 2D6, metabolic genotype, poor metabolizer, intermediate metabolizer, extensive, ultrarapid metabolizer

Introduction

Cytochromes are heme proteins, primarily responsible for the generation of ATP via electron transport. Several kinds of cytochrome exist and can be distinguished by spectroscopy (cytochromes a, b and d). A completely distinct family of cytochromes is known as the Cytochrome P450 (CYP450). CYPs metabolize thousands of endogenous and exogenous chemicals. In nature there are more than 200 P450 enzymes, of which 40 have been identified in humans. Six isoenzymes are responsible for at least 90% of enzymatic activity of the CYP450 (1A2, 3A4, 2C9, 2C19, 2D6, 2E1) [1 2] and Cytochromes 2D6 (CYP2D6) is one of the most studied in relation to genetic polymorphism. CYP2D6 gene

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(located on chromosome 22) has been reported to have more than 30 polymorphisms. This enzyme metabolizes approximately 25% of the drugs currently used. Psychiatric medications metabolized by cytochrome 2D6, may lead to different clinical response, according to patient genetic profiles. Several studies show that caucasian population is divided in different groups: 7% are poor metabolizers (having homozygous or heterozygous mutation leading to a lack of the enzyme in the liver), 36% are intermediate metabolizer (having a mutant allele and a functional allele of the gene, they are individuals who have a high risk of adverse reactions to the drug), 50% are extensive metabolizers (both alleles of the gene are active, it represents the percentage of normal individuals) and 7% are ultrarapid metabolizer (they show gene duplications with three or more functional alleles responsible for an increased expression of the gene, they are unlikely to benefit from the expected therapeutic effects) [1]. There is considerable variability in the distribution of CY2D6 among the different ethnical groups. The aim of the study is to understand the effects of different metabolic genotypes in terms of clinical effectiveness.

Materials and methods

We enrolled 80 psychiatric patients, 38 males, mean age at baseline time 43.7 years (range 17-78 years) with a diagnosis of panic disorder (n = 16), mood disorders (n = 36), mood disorders in comorbidity with panic disorders (n = 21) or psychotic disorders (n = 7). All patients were assessed with psychiatric evaluation and treated with psychopharmacological therapy (mood stabilizers, antipsychotics, antidepressants). They were subjected to a genotype analysis in order to evaluate the frequency of the allelic polymorphism of CYP2D6. The genotypic test was performed through a DNA amplification technique (PCR) and a microarray technology INFINTY BioFilmChip.

Results

We found that our sample was composed by 59% of extensive metabolizers (60% having significant side effects, 21% having good response and 19% therapeutic ineffectiveness). The 5% of our patients were poor metabolizers, the 25% of them having no benefits from pharmacological treatment, and the 75% presenting only side effects (hyperprolactinemia, weight gain, nausea, agitation). The clinical conditions of this group of patients improved by reducing drug doses. The 32% were founded to be intermediate metabolizers, with variable drug responses: the 64% of them showed side effects, the 28% had a therapeutic failure (these patients were all treated with carbamazepine and/or valproate, both acting as inducers of CYP3A4 substrates, thereby influencing the metabolism of alter substrate molecules of this isoenzyme) and just the 8% achieved a good response to therapy. This variability could be explained by several factors as personality, pharmacological interactions and compliance to therapy. Finally, the 5% were ultra rapid metabolizers, half of them having no benefits from the pharmacological treatment and the other half showing only side effects.

CYP2D6 Phenotype distribution in our sample

Poor Metabolizers (PM)	n. 4
Intermediate Metabolizers (IM)	n. 25
Extensive Metabolizers (EM)	n. 47
Ultrarapid Metabolizers (UM)	n. 4

Conclusions

The metabolic genotype of CYP2D6 is directly linked to pharmacotherapy's effectiveness.
The results show a good correlation between genotype and clinical phenotype in all groups except for extensive metabolizers (60% of this group developing major side effects). This result may be due to pharmacokinetic interactions between drugs able to induce or inhibit the specific isoenzyme when patients are treated with polypharmacy [3] and to the high prevalence (46%) of patients with anxiety disorder linked to farmacofobia (having an increased subjective perception of side effects). Testing metabolic genotype of 2D6 in clinical practice could allow us to avoid the onset of side effects and the risk of toxicity as well as recurrent dose corrections and therapy's failure. Moreover, patient's genotyping could help us to customize and personalize therapies in terms of doses evaluating patient's genetic profile. Future, larger studies including also pharmacokinetics interactions, patient's compliance and race's genetic differences are warranted to better customize pharmacological therapies. In the future, in order to have a more comprehensive understanding of the clinical response, it would be helpful to determine the plasma levels of active drug compounds in each patient, relating pharmacokinetic parameters to genotypic characterization. It may allow us to predict the clinical response in that specific patient after drug administration.

Take home messages for psychiatric care

- Psychiatric medications metabolized by cytochrome 2D6, may lead to different clinical response, according to patient genetic profiles
- Patient's genotyping could help us to customize therapies in terms of doses and times on the basis of patient's genetic profile
- Testing metabolic genotype of 2D6 in clinical practice could allow us to avoid the onset of side effects and the risk of toxicity as well as recurrent dose corrections and therapy's failure

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PSYCHIATRIC AND MEDICAL COMORBIDITIES: OBSERVATIONAL STUDY ON POST-TRAUMATIC STRESS DISORDER, FOCUS ON HIGH BLOOD PRESSURE AND CARDIOVASCULAR DISEASES

Abstract

Brief introduction: People suffering from post-traumatic stress disorder have shown a higher mortality with respect to general population, mainly due to cardiovascular diseases (CVDs) [1]. Metabolic Syndrome and its components (abdominal obesity, high triglyceride levels, low HDL cholesterol levels, high blood pressure, high fasting blood sugar), in particular, are highly prevalent in people with PTSD [2]. We therefore proposed to observe and describe, in a sample of patients suffering from PTSD, the onset and the course of high pressure and other Metabolic Syndrome components potentially predictive of cardiovascular disease, and other medical diseases.

Materials and Methods: We collected a sample of 37 PTSD patients (average age of 52,7 ± 11,5 years) at the "National observatory for the victims of terrorism" at the Psychiatry Section Department in Siena during the years 2014-2015. In the whole sample the type of the event experienced falls into the category of "terrorist's attack". Patients were assessed through clinical interview, then specific tests were administered: Clinician-Administered PTSD Scale (CAPS) to confirm the diagnosis, Davidson Trauma Scale (DTS) to assess the disorder severity and Mini-International Neuropsychiatric Interview (MINI) to exclude other psychiatric comorbidities. Current and remote clinical informations on medical conditions were also collected, together with blood and instrumental examinations (e.g. electrocardiogram). On the basis of these data, we retrospectively studied the prevalence of high blood pressure as a predictive of cardiovascular diseases, as well as the prevalence of other medical diseases, subsequently comparing these percentages and observing the onset.

Conclusions: Our results suggest that the components of Metabolic Syndrome are highly prevalent in patients suffering from PTSD, thus confirming recent data from the Literature [2]. We underline a possible connection between PTSD and the onset of high blood pressure [3]. Routine screening and multidisciplinary management of medical and psychiatric conditions is needed. Future research should focus, therefore, on the potential role of unknown factors or mediators that might clarify the nature of this association, stressing on the important comorbidity between psychiatric diseases and medical conditions like gastrointestinal, and neoplastic disorders [4].

Key words: PTSD, comorbidities, high blood pressure, Metabolic Syndrome, CVDs

Introduction

Post-traumatic stress disorder (PTSD) can occur in individuals who have been exposed to traumatic experiences to self or to others, resulting in an emotional response involving fear, helplessness, or horror. Various

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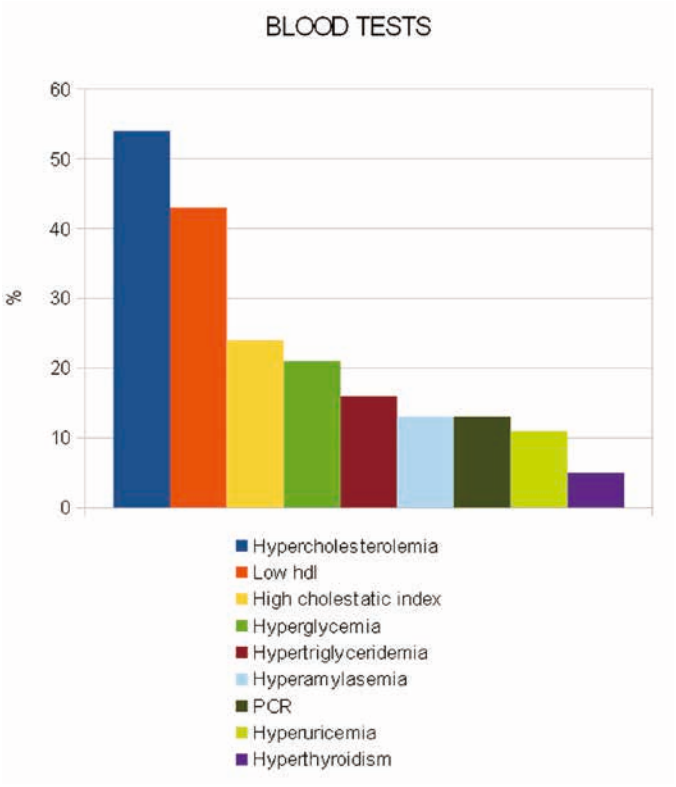

FIGURE 1.

types of trauma can trigger the disorder, including street or war combat, rape and other violent crimes, natural disasters, motor vehicle or industrial accidents. The response to trauma may include symptoms such as re-experiencing, nightmares, sleep disturbance, flashbacks and intense psychological or physiological distress. People suffering from post-traumatic stress disorder have shown a higher mortality with respect to general population, mainly due to cardiovascular diseases (CVDs) [1]; but also Metabolic Syndrome and its components (abdominal obesity, high triglyceride level, low HDL cholesterol level, high blood pressure, high fasting blood sugar), are highly prevalent in people with PTSD [2]. We therefore proposed to observe and describe, in a sample of patients suffering from PTSD, the onset and the course of high blood pressure and other Metabolic Syndrome components potentially predictives of cardiovascular diseases, and others medical diseases.

Materials and Methods

We collected a sample of 37 PTSD patients (24 male and 13 female, with a mean age of 52,7 ± 11,5 years and median of 57 years, as confirmed by meeting all the criteria of the CAPS (mean severity 84,2 ± 32,4) and DTS (mean severity 76,9+/-29), recruited at the "National observatory for the victims of terrorism" at the Psychiatry Section Department in Siena during the years 2014-2015. In the whole sample the type of the event falls into the category of "terrorist's attack"; the average duration of the disorder was 35 ± 14 years. Patients were assessed through clinical interview, then specific tests were administered: Clinician-Administered PTSD Scale (CAPS) to confirm the diagnosis, Davidson Trauma Scale (DTS) to assess the disorder severity and Mini-International Neuropsychiatric Interview (MINI) to exclude other psychiatric comorbidities. Current and remote clinical informations on medical conditions were also collected, together with blood and instrumental examinations (e.g. electrocardiogram). On the basis of these data, we ret-

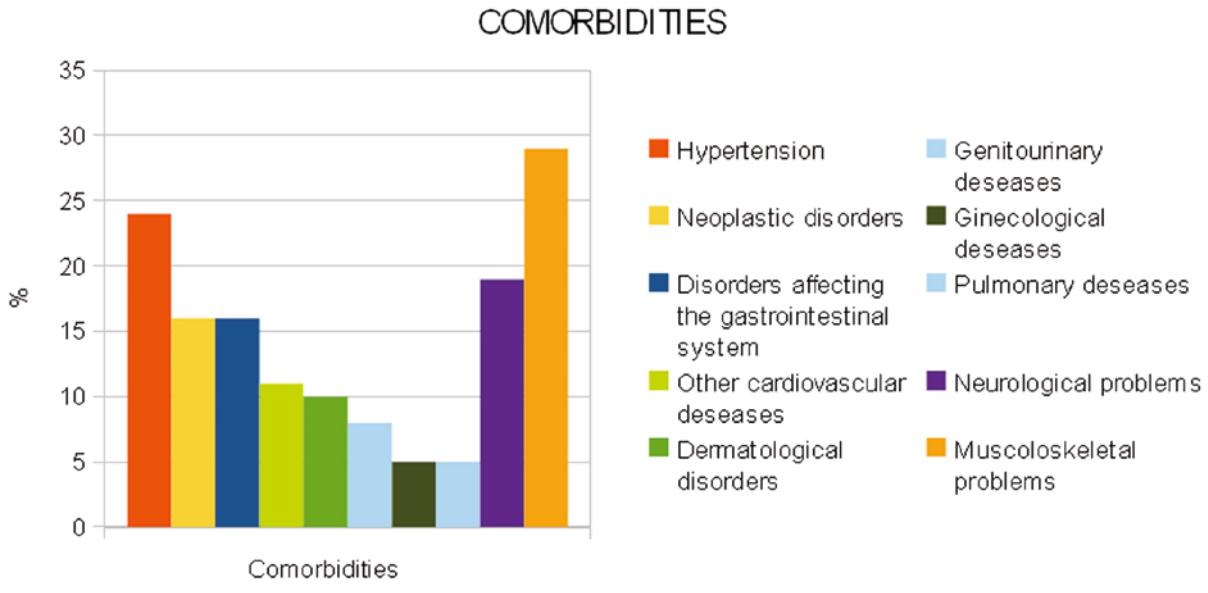

FIGURE 2.

rospectively studied the prevalence of high blood pressure as a predictive of cardiovascular diseases, as well as the prevalence of other medical diseases, subsequently comparing these percentages and observing the onset.

Results

In our population we found high prevalence of medical comorbidities. In blood tests (Figure 1) we found presence of hypercholesterolemia in 54% of patients, low HDL cholesterol level in 43% of patients, high cholestatic index in 24% of patients; hyperglycemia in 21% of patients suggesting the presence of diabetes, hypertriglyceridemia in 16% of patients, hyperamylasaemia and high inflammatory indexes (PCR, fibrinogen) in 13% of patients. Moreover, 11% of the sample showed hyperuricemia, 5% had laboratory findings of hyperthyroidism. As regards clinical assessment (Figure 2), 24% of the sample presented hypertension (11% others cardiovascular diseases: Takotsubo cardiomyopathy, angina pectoris, ECG signs of ischemia, venous stasis), 16% presented disorders affecting the gastrointestinal system (mostly GERD and *H. pilory gastritis*), 16% neoplastic diseases, 10% presented dermatological disorders, 8% presented genitourinary diseases, 5% presented pulmonary diseases (such as asthma) and 5% gynecological diseases. Furthermore, we found an high prevalence of neurological (19%) or muscoloskeletal problems (29%) mostly direct consequences of the physical trauma. If we analyze the patients with high blood pressure (24% of prevalence in our population: 8 male and 1 female), we observe that the totality of the patients develops high blood pressure after the traumatic event, and hypertension as cardiovascular desease. The 55,5% within two years after the traumatic event, the other part more than ten years later.

Conclusions

Our results suggest that the components of Metabolic Syndrome are highly prevalent in patients suffering from PTSD, thus confirming recent data from the Literature [2]. We underline a possible connection between PTSD and the onset of high blood pressure [3]. Routine screening and multidisciplinary management of medical and psychiatric conditions is needed. Future research should focus, therefore, on the potential role of unknown factors or mediators that might clarify the nature of this association, stressing on the important comorbidity between psychiatric diseases and medical conditions, like gastrointestinal and neoplastic disorders [4].

Take home messages for psychiatric care

- The components of Metabolic Syndrome are highly prevalent in patients suffering from PTSD
- We underline a possible connection between PTSD and the onset of high blood pressure as a predictor of CVDs
- Unknown factors or mediators might clarify the nature of this association, stressing on the important comorbidity between psychiatric diseases and medical conditions, like gastrointestinal and neoplastic disorders

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