Cannabis, nicotine and the negative symptoms of schizophrenia: Systematic review and meta-analysis of observational studies

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ABSTRACT

Despite the high prevalence in patients with schizophrenia, the association of cannabis and nicotine use with negative symptoms remains unclear. We performed a meta-analysis of observational studies addressing the association of cannabis and nicotine use with negative symptoms. Twenty cannabis studies (n = 2611) and 45 nicotine studies (n = 8942) were analyzed. There was no significant effect for current cannabis use alone or in combination with other substances. However, recently abstinent users of cannabis showed less severe negative symptoms than nonusers. Nicotine users were not different from nonusers with respect to negative symptoms. With respect to positive symptoms, very small increases were found for cannabis users and patients using nicotine along with other drugs. In conclusion, while patients with schizophrenia who use cannabis did not differ from nonusers, recently abstinent patients showed less severe negative symptoms than nonusers. This finding suggests that cannabis-using patients might be less susceptible to the development of negative symptoms. The amotivational effects of cannabis may obscure these differences in current users.

1. Introduction

Individuals suffering from schizophrenia and related disorders have a high prevalence of substance use disorders (Hunt et al., 2018). Epidemiological studies consistently report a higher lifetime prevalence rate of smoking (De Leon and Diaz, 2005d; Kotov et al., 2010) and cannabis use in patients with schizophrenia compared to the general population (Green et al., 2005). Patients with schizophrenia who use cannabis present higher relapse rates, longer hospital admissions, and more severe positive symptoms than individuals who discontinue cannabis use and those who are nonusers (Schoeler et al., 2016).

The association of comorbid substance use with negative symptoms has received less interest, although negative symptoms have a strong impact on functional outcome and remain difficult to treat (Galderisi et al., 2018). The negative symptoms of schizophrenia include blunted affect, alopecia, asociality, avolition, and anhedonia (Guessoum et al., 2020), which can be organized along the two dimensions diminished expression and apathy (Bègue et al., 2020). Negative symptoms be classified as primary or secondary (Kirkpatrick, 2014; Kirschner et al., 2017). Primary negative symptoms are thought to be intrinsic to schizophrenia, while secondary negative symptoms can be caused by positive symptoms, depression, side effects and substance abuse. The hypothesis of cannabis as a potential cause for secondary negative symptoms was initially based on observations of an amotivational syndrome in otherwise healthy individuals who are chronic cannabis users (Pacheco-Colon et al., 2018; Rovai et al., 2013). Cannabis may also exert an amotivational effect in patients with schizophrenia and thus be a cause for secondary negative symptoms (Kirkpatrick, 2014; Kirschner et al., 2017). Following this argument, one would expect more prominent negative symptoms in cannabis-using patients with schizophrenia than in nonusers.

This pattern has yet to be confirmed by the literature. An earlier meta-analysis by Potvin and colleagues studied the association between substance use disorders and negative symptoms (Potvin et al., 2006) and found a lower severity of negative symptoms across different substances of abuse. In a subgroup analysis, fewer negative symptoms were found in patients with cannabis use disorders than in those without cannabis use disorders. However, in a more recent meta-analysis including more studies and excluding patients with previous substance use, Large and colleagues did not find an association between current substance use (specifically cannabis use) and negative symptoms (Large et al., 2014). In summary, the existing meta-analyses do not suggest a higher level of negative symptoms in patients with schizophrenia who use cannabis, but they were based on a limited number of available studies that did not allow us to distinguish between patients using cannabis only and patients using cannabis as a main drug of choice.
Moreover, while data suggest a limited effect of cannabis discontinuation on negative symptoms (Schoeler et al., 2016), to the best of our knowledge, there is no systematic review of negative symptoms in patients recently abstaining from cannabis use.

It is important to note that individuals with schizophrenia consume cannabis almost exclusively in the context of nicotine use (Volkow, 2009). Most research on the association between symptoms and nicotine use has not focused on negative symptoms but on cognitive dysfunction (Conti et al., 2019; Figueiredo et al., 2020). One recent meta-analysis reported more severe positive symptoms but similar levels of negative symptoms in smokers compared to nonsmokers (Huang et al., 2019). Of importance, no distinction was made in this study between patients using only nicotine and patients using nicotine along with other drugs.

It has been suggested that negative symptoms are associated with reduced dopaminergic neurotransmission in the mesolimbic and mesocortical systems (Howes and Kapur, 2009; Maia and Frank, 2017). The acute administration of cannabis, nicotine and other drugs of abuse can increase dopaminergic neurotransmission in these systems and could thus improve negative symptoms in the short term (Awad and Voruganti, 2015; Peters et al., 2020). However, chronic substance abuse has been suggested to impair dopaminergic neurotransmission and could have deleterious effects on negative symptoms (Diana, 2011).

To our knowledge, no joint meta-analysis of the association of cannabis and nicotine with negative symptoms has been conducted thus far. The previous meta-analyses examining substance use disorder applied restrictive criteria, and therefore, only a few studies specific on cannabis use were retained (Large et al., 2014; Potvin et al., 2006). Furthermore, in these previous studies, no distinction could be made between populations consuming only cannabis and/or nicotine and populations using other substances such as alcohol, stimulants and opioids. Therefore, this systematic review investigates the relationship of cannabis and nicotine, used alone or mixed with other substances, with negative and positive symptoms of schizophrenia. In addition, we aimed to perform an analysis of negative symptom severity in persons recently abstaining from cannabis or nicotine use.

2. Methods

2.1. Selection procedures

This systematic review was conducted according to the PRISMA guidelines for systematic reviews and meta-analyses (Moher et al., 2009) (see supplementary methods S1). To account for aspects specific to observational studies, we also followed the MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (Stroup et al., 2000) (see supplementary methods S2). The study protocol can be found in the supplementary material (see supplementary methods S3).

2.2. Search strategies

Literature searches were conducted using Medline, PubMed, EMBASE, Psychnfo and PsycaRTICLE from 2 August to 14 September 2019. The following terms, combining key words and MeSH terms, were used: (schizo* or psychosis or psychotic) AND (marijuana or cannabis or cbd or cannabinoid or tetrahydrocannabinol or the or nicotine or tobacco or smoking). The search was restricted to articles in English and studies using humans. Additional studies were identified by cross-referencing the included studies and prior reviews.

2.3. Selection criteria

Studies that met all the following criteria were included: a) available in English; b) included inpatients or outpatients aged greater than 18 years with a DSM (American Psychiatric Association, 1980; APA, 2000) or ICD (World Health Organization, 2004) diagnosis of schizophrenia, schizoaffective disorder, or related psychotic disorder; patients considered stable (clinically and/or with at least 4 weeks of treatment with an antipsychotic medication); c) an observational study (cohort studies, case-control studies and cross-sectional studies) or a clinical trial reporting a baseline measurement; d) reported current nicotine or cannabis use either alone or as main drug of choice; e) specified whether patients were abstinent at the time of evaluation; and f) reported a baseline negative symptom score.

Studies that met any of the following criteria were excluded: a) meta-analyses, reviews, case reports, posters; b) reported populations with other diagnoses (in particular, a substance-induced disorder) and patients with first-episode psychosis; c) articles with overlapping datasets (only the more relevant article was retained); and d) articles with nonexploitable datasets (e.g., lifetime estimation use of drug only). In case of exclusion, reasons were reported.

Two authors (M.S. and N.Z.) independently applied the inclusion criteria to the identified studies. Any discrepancies between the authors were resolved through discussion until consensus was reached.

2.4. Data extraction

To achieve a high standard of reporting and to assess study comparability, we performed a full-text review with a detailed analysis of each included study (see supplementary results. Table S1). Two authors (M.S. and N.Z.) independently performed data extraction. Discrepancies between the two authors were resolved upon a joint full-text analysis with the third author (K.S.). All extracted data were independently crosschecked by two authors (M.S. and N.Z.) before the calculation of outcome variables. If necessary, additional or missing information was obtained from the study authors.

For the primary outcome, we extracted the mean value and standard deviation at baseline (or the 1-time measure of cross-sectional studies) of negative symptom severity. A broad range of assessment instruments was considered: the negative subscale of the Positive and Negative Syndrome Scale (PANSS-N) (Kay et al., 1987), the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1989), the withdrawal/retardation factor of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) or any other validated scale for the assessment of negative symptoms. In a secondary analysis, we considered the negative symptom dimensions amotivation and diminished expression separately; amotivation was calculated as the sum of the global ratings of avolition/apathy and anhedonia/asociality, and diminished expression was calculated as the sum of blunted affect and alogia (Strauss et al., 2013). The SANS dimension scores were imputed using the correlation matrix for the SANS global domain scores from a dataset reported in a previous study (Bischof et al., 2016).

We considered positive symptoms at baseline (mean value and standard deviation) as secondary outcomes. Positive symptoms were assessed with the positive subscale of the PANSS (PANSS-P), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984), or the sum of the thinking/disturbance and hostile/suspiciousness factors of the BPRS.

Additionally, we extracted all baseline values for scales reporting depression scores (e.g., the Hamilton Rating Scale for Depression (HRSD)) and specific variables such as demographic information (e.g., age), disease information (e.g., treatments, duration of illness), study design (e.g., cross-sectional), and information on substance use (e.g., cigarettes per day, years and doses of consumption, mixed use of other substances).

2.5. Assessment of methodological quality

The included studies were assessed for methodological quality using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2013) modified version for each type of observational study retrieved (cross-sectional, case-
control and cohort studies). The NOS is based on three subscales concerning the selection of cases, their comparability with the controls and the ascertainment of the exposure. A star system is used to assess each quality item; the highest-quality studies are awarded up to nine stars. For each study type, we defined the mean score of all included studies as a cutoff to identify high-quality studies. Two authors (M.S. and N.Z.) independently performed assessments.

2.6. Statistical analysis

All statistical analyses were performed using Cochrane Collaboration software, Review Manager (RevMan, version 5.3) and Stata software (version 16.0).

Our primary goal was to examine the association between cannabis and nicotine use and negative symptoms. We distinguished studies where nicotine alone (mostly tobacco) or cannabis and nicotine were used by patients from studies where other drugs were used or combined with these drugs (e.g., alcohol, amphetamines, hallucinogens), as these drugs have different effects on the brain. Accordingly, we defined four different subgroups of drug use: ‘cannabis and nicotine’, ‘cannabis as a main drug of choice’, ‘nicotine only’ and ‘nicotine as a main drug of choice’. We defined the ‘main drug of choice’ as either the drug the user reported as preferred or as the drug considered to be the main drug by the clinician rater. In addition, in almost all studies dependence criteria were fulfilled only for the main drug of choice. In the few studies including patients fulfilling dependence criteria for more than one substance, only a minority of patients was concerned. For a detailed description of drug use patterns in each study see supplementary table S1.

An additional subgroup consisted of studies including patients with ‘recent cannabis abstinence’, which corresponds to the absence of cannabis consumption for at least the past 21 days (recent cannabis abstinence). We intended to create an equivalent group for recent nicotine abstinence, but only two studies addressed the question, and the available data did not allow us to perform a meta-analysis (Esterlis et al., 2014; George et al., 2002).

In a first main analysis, we focused on cannabis use and included the subgroups ‘cannabis and nicotine’ and ‘cannabis as a main drug of choice’; then, we compared these results with those of the ‘recent cannabis abstinence’ group. In a second main analysis, we focused on nicotine use and included the subgroups ‘nicotine only’ and ‘nicotine as a main drug of choice’.

Since all included studies reported a baseline or a single score for our outcomes of interest, we did not separate studies on the basis of their design. For the primary outcomes, different scales or versions of

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Fig. 1. Systematic review PRISMA flow-chart.
scales were used across studies, and we therefore used standardized mean differences of cross-sectional measurement (baseline scores for longitudinal studies). There were clear a priori reasons for assuming heterogeneity because studies differed in design, population and substance use. Therefore, we used a random-effects model for all analyses. To assess the statistical heterogeneity between studies, we used the I^2 statistic, which provides an estimate of the percentage of variability due to heterogeneity rather than chance alone (Higgins et al., 2003). The chi-squared test was used for significance testing.

A visual inspection of the funnel plots was used to detect publication bias (Sterne and Egger, 2001). The robustness of the conducted analyses was examined by conducting sensitivity analyses including only high-quality studies. Furthermore, meta-regressions for potential moderators were planned (quantity of drug used per day, years of drug consumption, Fagerström score).

3. Results

3.1. Literature search

After a careful assessment of the identified publications regarding our inclusion and exclusion criteria, 65 studies were included in the qualitative and quantitative analyses (Fig. 1). Detailed reasons for the exclusion of screened articles are reported in Fig. 1. Overall, 36 cross-sectional studies, 24 case-control studies, 3 cohort studies and 2 randomized controlled trials were included in our meta-analysis, with 45 studies for nicotine and 20 studies for cannabis.

3.2. Study characteristics

For cannabis, 20 studies were included, with 4 studies in the ‘cannabis and nicotine’ subgroup, 9 studies in the ‘cannabis as a main drug of choice’ subgroup, and 7 studies in the ‘recent cannabis abstinence’ subgroup. For cannabis, 14 studies used DSM-III/IV criteria for cannabis abuse. For the studies on cannabis abstinence, six of the seven studies used urine drug screening to assess abstinence (DeRosse et al., 2010), and most studies used a criterion of 28 days of cannabis abstinence for inclusion.

For nicotine, 45 studies were included, with 29 studies for the ‘nicotine only’ subgroup and 16 studies for the ‘nicotine as a main drug of choice’ subgroup. Most nicotine studies based their criteria for nicotine use on the self-reports of participants and on Fagerström scale scores (see Table S2). Eighteen studies included heavy smokers (≥20 cigarettes per day).

Negative symptoms were reported by all 65 studies, with 42 studies using the PANSS and 13 studies using the SANS to report results. Positive symptoms were reported by 42 studies; however, one study did not report exploitable results (Postma et al., 2006).

3.3. Participants’ characteristics

The total number of participants included in our meta-analysis was 11,553 patients, including 5736 in the ‘no drug’ arm and 5487 in the ‘drug’ arm, of which 330 were in the ‘recent cannabis abstinence’ group. Most participants in the drug arm were male (76.1 %), while the proportion was balanced in the no drug arm (50.5 %). The United States of America had the highest number of studies (n = 14), followed by Germany (n = 8) and China (n = 7). The Chinese studies were notable due to the absence of cannabis studies and the low inclusion of women in the nicotine studies (9.3 % in the drug arms versus 39.7 % in the no drug arms of three studies). The mean age was 27.7 ± 3.23 years for the drug arm and 31.5 ± 5.05 years for the no drug arm of the cannabis studies. For nicotine studies, the mean age was 42.02 ± 4.90 years for the drug arm and 40.1 ± 6.05 years for the no drug arm.

In cannabis and nicotine studies, the assessment of substance use was based only on patient self-reports or medical records in most studies (n = 30 and n = 8, respectively), while some studies used a urine drug screening test (n = 7 and n = 6, respectively). Detailed information on cigarette consumption was available for 23 nicotine studies reporting a mean consumption of 21.3 ± 6.2 cigarettes per day. In 18 nicotine studies, participants consumed at least 20 cigarettes per day (see Table S2).

In all cannabis studies, cannabis was consumed with tobacco. The grams per day of cannabis was rarely reported (n = 5). Most case-control studies had age- and gender-matched cases and controls; additionally, some studies used years of education and illness duration as matching variables (see Table S1).

3.4. Methodological quality of studies

Based on the three different modified versions of the NOS for each type of observational study (see Table S3), the average scores for cross-sectional, case-control and cohort nicotine studies were 8.25, 7.3 and 6.5 points, respectively. For cannabis, only cross-sectional and case-control studies were available, which both had an average score of 7.8. Additionally, only one cohort was available for cannabis, and its quality was comparable to the two other cohort studies for nicotine.

These average scores were used as cutoffs to distinguish high-quality from low-quality studies. In sum, 17 out of 45 nicotine studies and 14 out of 20 cannabis studies were considered high-quality studies.

3.5. Quantitative outcomes

3.5.1. Association between current cannabis use and negative symptoms

The overall results for current cannabis users showed that there was no significant difference in negative symptom scores between the ‘cannabis use’ arm and the ‘no drug’ arm (SMD, 0.01; 95 % CI, -0.11 to +0.13; p = 0.83) (Fig. 2). Low overall heterogeneity (I^2 = 8%) and an absence of between-subgroup heterogeneity (I^2 = 0%) were observed, suggesting that the ‘cannabis and nicotine’ and ‘cannabis as main drug of choice’ groups were not differentially associated with negative symptoms (see below). An analysis of the corresponding funnel plot indicated that there was no publication bias (see Fig S1).

The ‘cannabis and nicotine’ subgroup did not have a significantly higher association with negative symptom scores than the ‘no drug’ group (SMD, -0.09; 95 % CI, -0.49 to +0.32; p = 0.68), and there was no within-subgroup heterogeneity (I^2 = 0%). There were no significant results for ‘cannabis as a main drug of choice’ (SMD, 0.01; 95 % CI, -0.15 to +0.17; p = 0.92).

3.5.2. Association between recent cannabis abstinence and negative symptoms

Compared to the ‘no drug’ arm, less severe negative symptoms were found in the ‘recent cannabis abstinence’ group, with a moderate effect size (SMD, -0.35; 95 % CI, -0.58 to -0.12; p = 0.003) and moderate heterogeneity (I^2 = 40 %). An analysis of the corresponding funnel plot indicated that there was no publication bias (see Fig S2).

A sensitivity analysis revealed that the study by De Rosse and colleagues (DeRosse et al., 2010) was mostly responsible for this heterogeneity. Excluding this study decreased the heterogeneity (I^2 = 8%), and a moderate effect size was found (SMD, -0.46; 95 % CI, -0.70 to -0.22; p = 0.0002).

3.5.3. Association between current nicotine use and negative symptoms

The overall results showed no difference in negative symptom scores between nicotine users and nonusers (SMD, 0.03; 95 % CI, -0.06 to +0.12; p = 0.55) (Fig. 3); the effect size was close to zero. A high level of overall heterogeneity (I^2 = 65 %) was observed, and the absence of between-subgroup heterogeneity (I^2 = 0%) indicates that the ‘nicotine only’ and ‘nicotine as a main drug of choice’ subgroups were not differentially associated with negative symptoms (Fig. 3). An inspection of the funnel plot indicated that there was no publication bias (see Fig S3).
3.5.4. Association between current cannabis use and positive symptoms

Overall, the results reveal that current cannabis users report higher levels of positive symptoms than nonusers; this association was marginally significant (p = 0.05), and the effect size was small (SMD, 0.11; 95% CI, -0.00 to +0.23; p = 0.05). A low overall level heterogeneity was observed (I² = 10%), and there was no between-subgroup heterogeneity (I² = 0%) (Fig. 4).

The corresponding funnel plot indicated that there was no publication bias (see Fig S4). No significant association with positive symptoms was found in the ‘cannabis and nicotine’ subgroup (SMD, 0.12; 95% CI, -0.28 to +0.53; p = 0.56; I² = 0%) or in the ‘cannabis as a main drug of choice’ subgroup (SMD, 0.13; 95% CI, -0.02 to +0.27; p = 0.16; I² = 30%).

3.5.5. Association between recent cannabis abstinence and positive symptoms

The ‘recent cannabis abstinence’ subgroup did not report different levels of positive symptoms than the ‘no drug’ arm (SMD, 0.17; 95% CI, -0.11 to +0.45; p = 0.24), and high heterogeneity was observed (I² = 58%). One study was responsible for the high heterogeneity (Schnell et al., 2009). Excluding this study reduced the heterogeneity (I² = 0%), and the results remained nonsignificant (SMD, 0.08; 95% CI, -0.07 to +0.23; p = 0.31). An analysis of the corresponding funnel plot indicated that there was no publication bias (see Fig S5).

3.5.6. Association between current nicotine use and positive symptoms

For the nicotine overall results, we found that nicotine users reported significantly more severe positive symptoms than nonsmokers; the effect size was small (SMD, 0.15; 95% CI, +0.07 to +0.23; p < 0.001). A high level of overall heterogeneity was observed (I² = 57%), and a low level of between-subgroup heterogeneity was observed (I² = 23%) (Fig 5).

The nicotine subgroup analysis suggests that this effect is more strongly driven by the ‘nicotine as a main drug of choice’ subgroup, with a small effect size (SMD, 0.19; 95% CI, +0.10 to +0.28; p < 0.0001) and moderate-to-high within-subgroup heterogeneity (I² = 51%). The ‘nicotine only’ subgroup was not associated with positive symptoms (SMD, 0.09; 95% CI, -0.05 to +0.24; p = 0.2).
corresponding funnel plot indicated that there was no publication bias (see Fig S6).

3.5.7. Sensitivity analysis for negative symptoms including only high-quality studies

The identified cutoff values were applied to distinguish low- and high-quality studies for each type of observational study (see Table S3).

For current cannabis users, high-quality studies (n = 8) presented similar findings, with no significant results for the overall groups (SMD, 0.08; 95 % CI, -0.02 to +0.18; p = 0.14) and no within-subgroup or between-subgroup heterogeneity (I^2 = 0%). For the ‘recent cannabis abstinence’ group, when considering only high-quality studies (n = 5), a slightly larger effect size was found (SMD, -0.44; 95 % CI, -0.73 to -0.14; p = 0.004), and low-to-moderate heterogeneity was observed (I^2 = 27 %).

In addition, for nicotine, the results for negative symptoms remained similar when including only high-quality studies (n = 17). No association with negative symptoms was observed in the overall results (SMD, 0.04; 95 % CI, -0.06 to +0.15; p = 0.42) or for the subgroup analyses (see Table S4).

Fig. 3. Forest plot for overall and subgroup relationship between ‘nicotine only’ and ‘nicotine as a main drug of choice’ with negative symptoms.
3.5.8. Sensitivity analysis for positive symptoms including only high-quality studies

The same method was applied to studies reporting positive symptom scores to distinguish low- and high-quality studies.

For cannabis studies, when focusing on high-quality studies (n = 7), the borderline significant results became nonsignificant (SMD, 0.07; 95 % CI, -0.03 to +0.17; p = 0.18), and there was no between-subgroup heterogeneity ($I^2 = 5.4 \%$) (see Table S4). For the ‘recent cannabis abstinence’ group, the results were unchanged (SMD, 0.23; 95 % CI, -0.23 to +0.69; p = 0.32), but there was a higher level of heterogeneity ($I^2 = 69 \%$).

For nicotine, similar results were found when focusing only on high-quality studies (see Table S4).

3.5.9. Further sensitivity and moderator analyses

Several additional analyses were conducted to assess whether the results for negative or positive symptoms depended on the characteristics of the participants, study designs, and drugs according to each subgroup; these factors have no effect on the results (see Table S4). For nicotine studies, we did not find a moderating effect of the Fagerström score, the number of cigarettes per day or years of tobacco consumption (see Fig S7 to S11).

3.5.10. Analyses of additional outcomes

Additional outcomes included the PANSS general psychopathology domain and depression scores in the subset of studies in which these measures were available. For general psychopathology, no significant association was found for current cannabis users (SMD, 0.08; 95 % CI, -0.02 to +0.19; p = 0.68), the ‘recent cannabis abstinence’ group (SMD, 0.04; 95 % CI, -0.44 to +0.51; p = 0.88) or for nicotine users (SMD, 0.03; 95 % CI, -0.12 to +0.18; p = 0.67) in the overall and subgroup analyses (see Fig S12 and S13). For the depression scores, no significant association was found for current cannabis users (SMD, 0.07; 95 % CI, -0.19 to +0.32; p = 0.92). For the ‘recent cannabis abstinence’ group, only one study was available that suggested that this group shows less severe negative symptoms than nonusers (SMD, -0.53; 95 % CI, -1.01 to -0.05; p = 0.03). No significant association was found for nicotine studies (SMD, 0.09; 95 % CI, -0.04 to +0.23; p = 0.16) in the overall and subgroup analyses (see Fig S14 and S15).

An analysis of the amotivation and diminished expression dimensions of negative symptoms was also conducted for all cannabis studies, but overall, only four studies reported sufficient data (see Fig S16). Therefore, no conclusions can be drawn about the differential associations of the cannabis user and the recent abstinence group with the two negative symptom dimensions. Only one nicotine study reported detailed SANS results; therefore, it was not possible to conduct a meta-
analysis. We further conducted several analyses to compare the characteristics of participants, studies, and drugs according to each subgroup (see Table S5). It was not possible to perform an analysis of specific types of positive symptoms (e.g., hallucination vs delusions), because in almost all studies only global positive symptoms were reported.

Finally, we compared demographic and clinical characteristics between substance users and nonusers (see Table S5). Both nicotine and cannabis users were more likely to be male. Cannabis users but not nicotine users had a younger age of onset of schizophrenia. Both active nicotine and cannabis users did have less years of education than nonusers. However, this was not the case in the small sample of cannabis abstainers. Finally, nicotine users, cannabis users and cannabis abstainers did not differ significantly from nonusers regarding anti-psychotic dose equivalents.

4. Discussion

4.1. Summary of the main findings

To our knowledge, this is the first meta-analysis of observational studies that focuses on the link between negative symptoms, cannabis and nicotine. Novel results are revealed based on a pool of more than ten thousand patients. Current non-abstinent cannabis users were not different from nonusers with regard to negative symptoms. Recently abstinent cannabis users show less severe negative symptoms compared to nonusers. Since nicotine was consumed by all participants in all cannabis studies, it is important to note that no association was found between nicotine use and negative symptoms. Thus, our findings support a specific effect of cannabis abstinence on negative symptoms.

Regarding positive symptoms, we observed borderline significant results with a very small effect size, suggesting a possible association with current cannabis use; however, this effect became nonsignificant when including only high-quality studies. In addition, we found that nicotine users reported higher levels of positive symptoms than nonusers, a result that had a very small effect size and was essentially driven by the 'nicotine as main drug of choice' group.

4.2. Association between cannabis use and negative symptoms

For cannabis, the overall results revealed the absence of a specific association between current cannabis use and the severity of negative symptoms. No difference was found between the subgroup using only cannabis and nicotine and the subgroup using cannabis as a main drug of choice.

These findings are consistent with the meta-analysis by Large and colleagues (Large et al., 2014) that also reported no significant differences between current cannabis users and nonusers. The similarity of the results is of note because there were considerable differences in the methods and included studies. Overall, we included a larger set of studies, but we restricted the included groups to patients with schizophrenia and excluded patients with broad first-episode psychosis. An earlier meta-analysis by Potvin and colleagues (Potvin et al., 2006) also restricted the inclusion criteria to patients with schizophrenia and suggested that cannabis users would show less negative symptoms than nonusers. However, only three cannabis studies could be included in that meta-analysis, and in one study, subjects had to be abstinent for at least three weeks. Overall, our study does not confirm Potvin and colleagues findings and shows that for patients with schizophrenia, there does not seem to be a significant difference in the severity of negative symptoms between current cannabis users and nonusers.

A key finding of the present study is the observation that patients with schizophrenia and chronic cannabis use who have recently stopped using cannabis show less severe negative symptoms than patients with schizophrenia who do not use cannabis. To the best of our knowledge, this finding has not yet been reported in a meta-analysis of cross-sectional data. Some evidence comes from a meta-analysis of longitudinal studies that showed a small trend-level effect, suggesting that cannabis discontinuers show less severe negative symptoms than continuous users and nonusers (Schoeler et al., 2016). A recent poster by Ihler and colleagues reported that experiential negative symptoms related to amotivation improved after 12 months of follow-up in the group who discontinued cannabis compared to continued use (Myhre Ihler et al., 2019).

The findings for recent cannabis abstainers have to be considered with caution, because most studies had small sample size and the only large study reported a small effect size (De Rosse et al. 2010). However, the study was rated as having a high risk of bias and the low effect size in this study can be explained by less restrictive criteria for abstinence, in particular the lack of urine drug screening to verify abstinence. Importantly, all of the abovementioned results remained largely unchanged when restricting the analyses to high-quality studies. An important limitation of our results concerns the fact that it was not possible to conduct a meta-regression with the amount of cannabis used as an independent variable because only a few studies reported the grams of cannabis used per day, and only one study estimated the THC content. However, the dose dependence of cannabis effects remains of major importance and needs further evaluation with respect to negative symptoms (Ramesh et al., 2013).

4.3. Association between nicotine and negative symptoms

Our results suggest that patients with schizophrenia who use nicotine do not report different levels of negative symptoms than nonusers, with the effect size being close to zero. This finding is consistent with a recent meta-analysis by Huang and colleagues that also found no association between nicotine and negative symptoms (Huang et al., 2019). Here, we expand the findings by Huang et al. by using a larger sample of studies to show that this absence of an association occurs in studies including patients using nicotine only as well as in studies including patients using nicotine as a main drug of choice.

The available data did not allow us to perform a meta-analysis of nicotine abstainers compared to nonsmokers. Boggs and colleagues report a small nonsignificant decrease in negative symptoms following one week of nicotine abstinence (Boggs et al., 2018), indicating that further research is needed.

4.4. Mechanisms linking cannabis use and negative symptoms

Here, we report that patients with schizophrenia who current use cannabis do not differ from nonusers regarding the severity of negative symptoms. One interpretation of the absence of an association in the current users would be that cannabis simply does not exert any effects on negative symptoms. While this interpretation would not be in line with the hypothesis concerning the amotivational effects of cannabis use, it must be considered that the evidence for the negative effects of cannabis on motivation remains heterogeneous (Pacheco-Colon et al., 2018). It may also be difficult to detect the effects of cannabis consumption on negative symptoms because patients with schizophrenia will often suffer from a combination of primary and secondary negative symptoms. Thus, the potential amotivational effects of cannabis as a secondary symptom may account for only a part of the overall negative symptomatology shown by the individual patient. Alternatively, it is conceivable that in chronic cannabis users with schizophrenia, the stimulating and blocking effects of cannabis on the reward system offset each other and result in the absence of an effect on negative symptoms (Colizzi and Bhattacharya, 2018; Lawn et al., 2016).

However, these considerations cannot account for the second important finding reported here, i.e., that recent cannabis abstainers show less severe negative symptoms than nonusers. This finding is consistent with the reduced susceptibility of developing negative symptoms among patients with schizophrenia who use cannabis. Previous reports
have suggested that cannabis-using patients with schizophrenia have better cognitive functioning than nonusers, particularly with respect to premorbid cognitive functioning (Ferraro et al., 2013; Schnell et al., 2009; Yucel et al., 2012). Furthermore, a recent study conducted by Mallet and colleagues has found that patients with heavy cannabis use before the onset of psychosis showed significantly less neurological soft signs, less negative symptoms and better cognitive functioning in different domains than their non-heavy user counterparts (Mallet et al., 2017). It has therefore been hypothesized that cannabis-using patients constitute a subgroup that has lower biological vulnerability, which also results in a reduced susceptibility to developing negative symptoms.

Another explanation suggests that cannabis-using patients might more easily access cannabis due to better premorbid social functioning, which could also be related to a reduced susceptibility to developing negative symptoms (Jockers-Scherubl et al., 2007; Potvin et al., 2006).

Thus, cannabis-using patients with schizophrenia have less severe negative symptoms when they abstain from the drug. When using the drug, this difference may be obscured by the amotivational effects of cannabis (Pacheco-Colon et al., 2018; Rovai et al., 2013). Importantly, the abstinence duration of at least three weeks required in the abstinence studies seems to be sufficient to alleviate the negative effects of cannabis on motivation. This timeframe is consistent with positron emission tomography studies in healthy cannabis users that show reduced dopamine release in the associative striatum in current users (van de Giessen et al., 2017). Interestingly, in earlier studies with the same minimum duration of abstinence as in our abstainer studies, dopamine release in the striatum was not different from nonusing controls (Urban et al., 2012). Therefore, the time period of abstinence required in our recent abstainer group is consistent the normalization of dopamine release in the striatum.

4.5. Association of cannabis with positive symptoms

We found a borderline significant association of current cannabis use with positive symptoms without significant subgroup differences between cannabis and nicotine groups and cannabis as the main drug of choice groups. However, the effect size was very small and might be of questionable clinical significance.

These results differ to some extent from those reported by Large and colleagues, who found a medium effect size for the association of current cannabis use with positive symptoms (Large et al., 2014). Several differences between the two meta-analyses must be noted. First, we included a larger number of studies than Large, but we did not include studies with patients experiencing broad first episode psychosis, which may lead to stronger effects of cannabis on positive symptoms. Second, in the first-episode studies included in the Large meta-analysis, not all patients were receiving antipsychotics. The fact that we were focusing on stabilized populations treated with antipsychotic medication might have led to a weaker association of cannabis with positive symptoms. Third, our analysis allowed us to differentiate the groups ‘cannabis and nicotine’ from cannabis as the main drug of choice, but this differentiation did not have an impact on effect size.

Furthermore, we were able to specifically address the recent cannabis abstainer group. In contrast to the findings for negative symptoms, this group did not significantly differ from the nonuser group. Overall, our results show only a very limited cross-sectional association between cannabis use and positive symptoms.

4.6. Association of nicotine with positive symptoms

Our results show that overall nicotine use is associated with more severe positive symptoms, although the effect size was very small. In the subgroup analysis, the effect was significant only for the ‘nicotine as a main drug of choice’ group. Importantly, this subgroup effect remained significant when considering only high-quality studies, while the overall effect became nonsignificant.

Huang and colleagues reported a somewhat larger effect size for the association of nicotine use with positive symptoms (Huang et al., 2019). Our meta-analysis included a larger number of important studies and allowed a clear distinction of ‘nicotine only’ and ‘nicotine as a main drug of choice’ subgroups. Our subgroup analysis suggests that the observed association with positive symptoms might be more strongly related to the concomitant use of other drugs along with nicotine. However, we cannot exclude the possibility that nicotine use alone could increase the severity of positive symptoms to some extent.

4.7. Mechanisms linking cannabis and nicotine use to positive symptoms

Our results only suggest a very limited cross-sectional association of continued cannabis use with positive symptoms. The acute psychosis-inducing effects of THC have been well documented and seem to at least be partially related to increased dopamine release in the striatum (Hindley et al., 2020). However, the long-term effects seem to depend on a large number of parameters, including the duration and intensity of the exposition as well as the proportion of THC and cannabidiol (Colizzi and Bhattacharyya, 2018; Di Forti et al., 2019). Our data suggest that the effects of ongoing cannabis consumption are to some extent offset by ongoing antipsychotic drug treatment.

Although our data provide little evidence for a specific association of nicotine use with positive symptoms, it has to be noted that there is some evidence that psychotic-like experience have been associated with the smokers’ status in the general population after adjustment for confounding factors (Bhavsar et al., 2018; Mallet et al., 2018). Moreover nicotine has been suggested to increase positive symptoms via increased dopamine release and the increased metabolism of antipsychotic drugs (Quigley and Maccabe, 2019). There was a small but highly significant association in the nicotine as the main drug of choice group. A mechanistic interpretation of the finding is difficult because substance use in this subgroup was very heterogeneous across the different studies.

4.8. Limitations

The main limitation of our meta-analysis is the nature of the included studies, which employed heterogeneous methods. It should be noted that the number of patients included was much higher in the nicotine groups than for the cannabis groups. Therefore, future studies with large sample size could change the results for cannabis users and recent abstainers. Nevertheless, this is the largest meta-analysis on the topic so far, and we were able to conduct sensitivity analyses including only high-quality studies that confirmed the main findings.

Several limitations concern the case and control definition, such as differences in population, inclusion criteria and methodology across the included studies. Although the proportion of male and female participants was balanced in the control arm, the proportion of male participants was higher in the drug arms. This outcome highlights an important issue because, at least for nicotine use, sex-specific associations with D2-type receptor availability have been suggested (Okiti et al., 2016). Nevertheless, the main results on nicotine were confirmed in a sensitivity analysis without the Chinese studies that almost exclusively included male smokers.

Another important limitation concerns the exposure. In the ‘cannabis and nicotine’ subgroup studies, controls were allowed to smoke in most studies, but only a few studies documented the amount of tobacco used or the severity of dependence. However, since no association with negative symptoms was found in the ‘nicotine only’ subgroup, the impact of this limitation seems weak. Other limitations need to be considered, such as the absence of a generally accepted definition for heavy smoking (Neumann et al., 2013) and very scarce information on the content of nicotine, the potency or the amount of THC and cannabidiol consumed as well as even the intensity of inhalation.
Furthermore, limitations regarding the outcome measurements must be considered. Most importantly, very little information was available on the apathy and diminished expression dimensions of negative symptoms. Therefore, the findings reported have to be interpreted with caution. It was not possible to conduct a meta-analysis on the five domains of negative symptoms. In addition, there were limitations in the data for secondary outcomes, such as depression and antipsychotic treatment. Therefore, we cannot determine the extent to which our findings are related to an association of drug use with negative symptoms secondary to depression or medication side-effects.

Finally, it must be emphasized that the cross-sectional approach of this meta-analysis does not allow for a causal interpretation of the observed associations.

5. Conclusion

While patients with schizophrenia currently using cannabis did not differ from nonusers, recently abstinent patients showed less severe negative symptoms than nonusers. This finding suggests that cannabis using patients might be less susceptible to the development of negative symptoms. The amotivational effects of cannabis may obscure these differences in current users. However, three weeks of abstinence seem to be sufficient to alleviate the amotivational effects. To investigate the potential causal nature of these effects, longitudinal studies are needed. No specific association of nicotine with negative symptoms was found, but the effects of nicotine abstinence on negative symptoms require further investigation. For positive symptoms, we observed smaller effects of cannabis and nicotine than in previous studies, which might be related to our criteria restricting studies to only those including patients with schizophrenia and antipsychotic drug treatment.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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