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A influência da intervenção de cessação tabágica nos sintomas depressivos em fumadores com história de depressão major: revisão sistemática / The influence of smoking cessation on depressive symptoms in smokers with a history of major depression: a systematic review

Março, 2022

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UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Psiquiatria

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

The influence of smoking cessation on depressive symptoms in smokers with a history of major depression: a systematic review

ORIENTADOR

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COORIENTADOR (se aplicável)

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DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☐

Faculdade de Medicina da Universidade do Porto, 22/03/2022

Assinatura conforme cartão de identificação: Pedro Nunes

The influence of smoking cessation on depressive symptoms in smokers with a history of major depression: a systematic review

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ABSTRACT

The presence of depression increases the risk for smoking and vice versa, according that half of smokers seeking treatment have a history of depression. Depressive states can be provoked or exacerbated by smoking cessation and there is consistent evidence in that direction. It must be taken into account that smokers are not a homogeneous group so that it is important to develop different smoking cessation interventions for specific groups, such as people with past or current major depression. The aim of this review was to summarize the findings from published studies to reach a conclusion of which smoking cessation interventions are more efective in reducing depressive symptoms in this specific population and if smokers who successfully abstain are at risk of increased depressive symptomatology. A systematic review was conducted based on PRISMA´s guidelines. A bibliographic search was made by quering Cochrane and PubMed databases from which were included eight papers. The majority found improvement of depressive symptomatology in the subgroup of smokers who attained to stop smoking. Moreover, SSRI treatment was associated with a reduction of depressive symptoms, in particular sertraline that reached statistical significance in reducing depressive symptomatology when compared with placebo. Even though it is not possible to draw definitive conclusions, this review highlights some evidence that smoking cessation intervention may be a realistic opportunity to improve depressive symptomatology and that active intervention with SSRI may be a big aid in treatment.

KEYWORDS: Smoking cessation; Major depressive disorder; Depressive symptoms.

1. MAIN TEXT INTRODUCTION

Depression and smoking are among the leading causes of disability and death in the world. The presence of one condition increases risk for the other according that half of smokers seeking treatment have a history of depression (Anthenelli et al., 2013). Several studies have shown that depressive states can be provoked or exacerbated by smoking cessation and there is consistent evidence that within days or weeks following smoking cessation depressed mood occurs (Berlin et al., 2010).

Besides that, it must be taken into account that smokers are not a homogeneous group so that it is important to develop different smoking cessation interventions for sprecific groups, such as people with past or current major depression. Major depression is associated strongly with smoking. A recent review showed that smokers with past major depressive disorder clearly have an increased risk for a new episode of major depression after quitting smoking. Other research pointed to the fewer functional cognitive coping skills patented by smokers with past major depression comparative to smokers without a life-time major depression. This hypothesis has led to several studies examining smoking cessation interventions that include strategies for managing depressive symptoms (van der Meer., 2010).

Scientific studies examining the influence of smoking cessation interventions on depressive symptoms in smokers with a history of major depressive disorder have been performed but no systematic review of this theme has been undertaken to date. Therefore, the aim of this study was to summarize the findings from published studies to reach a conclusion of which smoking cessation interventions are more effective in reducing depressive symptoms in this specific population and if smokers who successfully abstain are at risk of increased depressive symptomatology.

2. MATERIALS AND METHODS

The methodological approach used in this review was based in PRISMA`S guidelines, available at “prisma-statement.org”. Two authors independently (PN & MB) conducted a search of PubMed and Cochrane´s databases for publications that were related to smoking cessation and major depressive disorder. The only restriction was in terms of publication type: randomized controlled trials. The query used was: (Smoking

cessation OR smoking cessations OR stopping smoking OR giving up smoking OR giving up smokings OR quitting smoking) AND (Major depressive disorder OR major depressive disorders OR involutional paraphrenia OR involutional paraphrenias OR involutional psychosis OR involutional psychoses OR involutional depression OR involutional melancholia). In a first phase selection, repeated articles were sorted out, and the rest of articles were selected by title and abstract from the same query above.

In a second phase, selected articles were individually read and submitted to the following inclusion criteria: 1) population composed only of patients with major depressive disorder; 2) smoking cessation exclusive intervention; 3) depressive symptomatology as outcome. Articles in which population had other psyquiatric diagnoses or other mood diseases that not major depression were excluded, as were publications in which intervention was an healthy lifestyle promotion that includes but is not restricted to smoking cessation.

Data retrieved from each article included year of publication, country, methodology, population, type of smoking cessation interventions, criteria for classification of patients with MDD and to evaluate depressive symptoms, as well as key findings. Risk of bias was assessed by using "Revised Cochrane risk-of-bias tool for randomized trials".

3. RESULTS

3.1. LITERATURE SEARCH

From the initial search, 243 articles were selected. After the first phase selection, 52 articles followed to the second phase selection, resulting in 8 final articles that were included in this review (Fig.1).

From all articles, 6 were from United States of America (USA), 1 from Europe (Netherlands) and 1 from USA and seven other european countries.

All studies included were randomized controlled trials (RCT).

3.2. POPULATION

All studies were related to smokers with current or past major depressive disorder (MDD). The majority of it (6) included only smokers with past MDD, not current. Another one included a population of stably treated current or past MDD. Other was circumscribed to smokers with current MDD.

3.3. METHODOLOGY APPLIED

Regarding classification of patients with MDD, the unanimously used instrument was Structured Clinical Interview for DSM disorders (SCID for DSM), that was used in all 8 studies. One of these studies also used Hamilton Depression Rating Scale (HDRS) to include only participants who obtained a score of ≥14 on the HDRS.

In terms of the scales used to assess evolution of depressive symptoms, four studies used Beck Depression Inventory (BDI), among which one also used HDRS. The rest used SCID for DSM (one study), HDRS (one study) and Center for Epidemiologic Studies Depression Scale (CES-D, one study). Finally, another one study opted to use Montgomery-Asberg Depression Rating Scale (MADRS).

3.4. DEPRESSIVE SYMPTOMS

3.4.1. BY SMOKING STATUS

Firstly, the evolution of depressive symptoms over the time of the different studies was assessed without distinguishing types of interventions but comparing those who attained smoking abstinence with those who did not manage stop smoking.

Starting from this premise, five studies found improvement of depressive symptomatology over time in the subgroup of smokers who stopped smoking during the study period. On the other hand, those who tried to attain abstinence but lapsed did not replicate such results (Thorsteinsson et al., 2001; Brown et al., 2001; Burgess et al., 2002; van der Meer et al., 2010; Berlin et al., 2010).

Contradicting this findings, a study pointed that of the 34 who continued to smoke, 2 (6%) had symptoms of MDD during follow-up compared with 13 (31%) of those who stopped (Glassman et al., 2001).

The rest of studies did not compare participants who attained abstinance with those who did not (Glassman et al., 2001; Anthenelli et al., 2013).

3.4.2. BY TYPE OF INTERVENTION

3.4.2.1. SELECTIVE SEROTONINE REUPTAKE INHIBITORS (SSRI)

Three studies approached the effect of treatment with SSRI compared with placebo in depressive symptomatology. Two of them used sertraline as active intervention while the other used fluoxetine. In one study it was reached a sertraline treatment effect on HDRS for both abstainers and non-abstainers. In particular, in the subgroup of smokers who tried to attain abstinence but lapsed (non-asbtainers), sertraline reduced significantly HDRS compared with placebo (Berlin et al., 2010). In the other study in which the active intervention was sertraline, smokers who stopped smoking while on placebo were more likely to develop major depression during follow-up than those who stopped while taking sertraline. Thus, depression ocurred in follow-up in nine (43%) abstinent participants assigned placebo compared with four (19%) of those assigned sertraline (Glassman et al., 2001). Finally, the study in which active intervention was fluoxetine reached statistically significant decreases in self-reported measures of depression in the subgroup treated with fluoxetine. However, the comparison of change scores did not reveal a statistically significant difference between placebo and fluoxetine groups (Dalack et al., 1995).

3.4.2.2. NICOTINE / NICOTINE REPLACEMENT THERAPY (NRT)

One study compared active nicotine patches with placebo patches for two weeks plus a third week of placebo in both study arms and reached no evidence for either increased depression following cessation in the placebo group or antidepressive effects on mood in the nicotine group (Thorsteinsson et al., 2001). The other one study had varenicicline as NRT and placebo as control group. From this study, standardized assessment of mood levels showed no clinically relevant diferences between groups (Anthenelli et al., 2013).

NON PHARMACOLOGICAL

The remaining studies consisted of non pharmacological strategies for smoking cessation. One of it compared a mood management intervention with a proactive telephone counselling as control that consisted of strengthening stop-smoking skills, namely social support, increasing self-efficacy, self-rewarding and relapse prevention. On the other hand, the mood management intervention was an integration of control intervention with a mood management component. As a result, that seemed to be no intervention effect on change of depressive symptoms between experimental and control conditions (van der Meer et al., 2010). The other two studies consisted of cognitive-behavioral treatment for depression (CBT-D) compared with standard smoking cessation intervention (ST) and both reached similar findings. One found that CBT-D did not affect the course of depressive symptoms during smoking cessation (Burges et al., 2002). The other also failed to show any significant effect of treatment, as changes in depressive symptoms after quitting or prior to quit date did not differ by treatment condition. Even in the two subgroups that showed improved long-term abstinence, smokers with recurrent depression and heavy smokers, no relative advantage in regard to CBT-D was found (Brown et al., 2001).

3.5. RISK OF BIAS

By using “Revised Cochrane risk-of-bias tool for randomized trials”, two studies were classified as high risk of bias due to missing outcome data. In these studies, number of dropouts was relevant and were probably non-abstainer participants, being that in one of the studies were really heavy smokers, which can lead to an underestimation of depressive symptoms (Burgess et al., 2002; Berlin et al., 2010). Four studies were classified as some concerns also due to missing outcome data. However, in two of these the number of dropouts were similar between intervention and placebo (van der Meer et al., 2010; Anthenelli et al., 2013). In another study, the dropout rate was higher in the group receiving placebo (50%) than nicotine (22%), that may have masked the effects of smoking cessation on depressive symptoms but an analyses made comparing completers and non-completers failed to show any evidence in that direction because there were no baseline neither post-treatment diferences. Still in this study, it was classified as some concerns arising from the randomization process, because patients assigned to the active patch group had significantly higher scores on the baseline HDRS (Thorsteinsson et al., 2001). In the other of these four and similarly to the above, besides the possible underestimation of depressive symptoms, dropped out patients didnt`t have significant baseline diferences from the rest of participants (Glassman et al., 2001). Finally, two studies were classified as low risk of bias (Dalack et al., 1995; Brown et al., 2001).

4. DISCUSSION

Results in this systematic review reveal some interesting points, although it is difficult to draw definitive conclusions from the outcomes evaluated.

To begin with, the majority of studies found improvement of depressive symptomatology over time in the subgroup of smokers who stopped smoking during the study period (Thorsteinsson et al., 2001; Brown et al., 2001; Burgess set al., 2002; van der Meer et al., 2010; Berlin et al., 2010), while two studies did not compare depressive symptoms in smokers who attained smoking abstinence with those who did not attain (Dalack et al., 1995; Anthenelli et al., 2013). Only one study contradicted the trend, insofar as it pointed that depressive symptomatology increased in the subgroup who attained smoking abstinence relatively to the subgroup that did not (Glassman et al., 2001). Therefore, for this initial assessment, findings offer little support for the hypothesis that smoking cessation increases depressive symptoms in smokers with history of past or even current major depressive disorder. In fact, if smoking cessation causes depression in this specific population, we should have observed a clear decline in mood upon cessation, which we did not. In order to justify this findings, it is possible to hypothesize that patients who are capable of attaining smoking abstinence experience a sense of pride and achievement that is responsible for the reduction in depressive symptomatology. In contrast, mood deterioration in non-abstainers could be the result of disappointment with the failure of the quit attempt. Whether this effect is perpetuated in time, it is difficult to know since two of this studies followed participant`s evolution of depressive symptoms for a maximum of 2 weeks after quit date (Burgess et al., 2002) and 9 weeks post-quit date (Berlin et al., 2010). However, the other three made follow up times of 12 months, which is more reliable in terms of prolonged abstinence over time (Thorsteinsson et al., 2001; Brown et al., 2001; van der Meer et al., 2010).

It is possible to organize the studies included in this systematic review by type of intervention. Therefore, three studies were related to antidepressive treatment with SSRI (two used sertraline and one fluoxetine), two tested nicotine / nicotine analogue (varenicicline) and the other three were about non-pharmacological strategies of mood management. The fact that similar interventions produced similar outcomes is a factor that allows to draw some conclusions. In this regard, SSRI treatment was associated with an improvement in depressive symptoms (Dalack et al., 1995; Glassman et al., 2001; Berlin et al., 2010), being that in two of the three studies SSRI, in particular sertraline, reached statistical significance in reducing depressive symptomatology when compared with placebo (Glassman et al., 2001; Berlin et al., 2010). In the other

hand, neither nicotine / varenicicline studies were capable of producing clinically relevant diferences from placebo (Throsteinsson et al., 2001; Anthenelli et al., 2013), nor were the three studies that encompassed mood management therapy / CBD-T towards proactive telephone counselling / standard smoking cessation intervention (Brown et al., 2001; Burgess et al., 2002; van der Meer et al., 2010).

Besides being expectable that SSRI, in particular sertraline, produce a positive response in terms of depressive symptomatology, this antidepressive treatment has revealed itself an important aid in the subgroup of smokers who tried to attain abstinence but lapsed as indicated in Berlin et al.´s study (2010). This profile of smokers may possibly benefit from sertraline treatment insofar as it may help them leading with frustration of a failed quit attempt. Thus, it may reduce the negativity of the experience and help to motivate to a future new smoking cessation attempt. By Dalack et al.´s (1995) and Berlin et al.´s studies (2010) it is possible to speculate whether smokers assigned SSRI might undergo rebound depression when the drug was discontinued given the inexistence of post-treatment follow up time of the participants of this studies. However, Glassman et al.´s study (2001) followed up participants for 6 months after end of treatment and yet placebo, not antidepressant, was associated with an increased rate of follow-up depression (Glassman et al., 2001). Besides that, further studies with prolonged follow-up duration are needed to evaluate whether SSRI are capable of a time sustained response in terms of reduction of depressive symptoms in patients with history of major depressive disorder that are trying to stop smoking. It is well known that some smokers with a history of depression sense that cessation provokes depression, what causes them to fear trying to stop smoking. In this kind of patients, maintenance of antidepressive tratment with SSRI might be a better alternative to continued smoking, although we do not know whether such treatment would prevent smoking relapse. It is also important to refer that regardless of Dalack et al.´s study (1995) did not find significant advantage of fluoxetine treatment over placebo, the sample size was limited to only 39 participants and the treatment duration of 3 weeks could not be enough to see a response with fluoxetine.

The findings that nicotine and varenicicline had no clear antidepressive effects over placebo was unexpected, given that it is documented that nicotine may have antidepressive properties (Thorsteinsson et al., 2001). Furthermore, the hypothesis that depressed people use nicotine to enhance their mood, which is also referred in Thorsteinsson et al.´s study (2001), is not supported by the results of this study neither Anthenelli et al.´s (2013). In one hand, it is possible to point that nicotine´s study was limited by the low number of participants included (N=39), on the other hand varenicicline´s study was a larger one with a total of 525 participants so it is difficult to try to justify this unexpected findings by sample size. Further studies are needed to address this point.

The absence of an advantage of mood management strategy / CBT-D over proactive telephone counselling / ST may try to be explained by some points. To begin with, selection of samples of smokers for past MDD include many participants with minor disease, such as only one past episode. It is passible to be argueed that this ones may not be at increased risk for poor evolution of depressive symptoms and in this case may not benefit from addition of CBT-D / mood management. Another possible hypothesis is that it may not be feasible to treating depressive symptoms while concurrently initiating nicotine fading such as was done in Brown et al.´s study (2001) and Burges set al.´s study (2002), or while concurrently stopping smoking after a target quit day as van der Meer et al.´s study (2010). In this last referred study, the timing of post-quit day measurements of depressive symptomatology were made at 6 and 12 month follow up. As a result, it is possible to say that there may have been a reduction earlier in the study which was no longer apparent at 6 and 12 month. Despite that, Brown et al.´s study (2001) and Burgess et al.´s study (2002) measured depressive symptoms 1 month post-treatment and 2 weeks after quit date respectively, and did not reach different results. Future studies that evaluate the efficacy of mood management / CBT-D with specific subgroups of smokers with clearly specified risk profiles that predict poor response to ST related strategies

would probably make it easier to select the non pharmacological intervention that is more likely to benefit individual smokers.

Some limitations need to be aknowledged. First, only two search engines were used so it is not known to what extent a significant quantity of relevant articles were left out. This systematic review only included eight papers. Second, some studies included a small number of participants, in particular two. However, in the concern of a lesser generability of findings the most relevant is that in all studies smokers were recruited through adds on social media, or other means but all interested in smoking cessation and somehow motivated to stop smoking. Furthermore, participants were excluded if concurrently taking antidepressive medication or current dystimia, or substance abuse other than tobacco, or even psychotic features and others. Only one study included patients with current depression. Even though this restrictions aim to reduce confounding effect, it also contributes to the sample of participants not to be representative of the wider population. Moreover, this motivated patients belong to the mild or moderate spectrum of major depressive disorder in so that they represent a group more likely to be seen in a family practitioner´s than in a psychiatric´s office. Seen that, it is possible to argue that the influence of this smoking cessation trials in depressive symptoms may be generally overestimated. Studies that address the subset of smokers with severe major depressive disorder need to be developed. Another important point is that MDD is a dichotomous variable and does not differentiate smokers with a single episode from those with multiple episodes of MDD and there may be relevant differences between this groups that require specific treatment. Relatively to studies that addressed non pharmacological treatments, interventions as controls were not the same but very similar in order that this studies were analyzed together.

In conclusion, findings were consistent with other´s in literature that smoking cessation aids in psychiatric patients generally do not exacerbate psychiatric illness, in this particular case MDD. It is even possible to say that in a subset of mild to moderate patients with MDD motivated to quit smoking, smoking cessation may be a realistic opportunity to improve depressive symptomatology and that active intervention with SSRI may be a big aid in treatment. A future systematic review, with more studies included and new scientific evidence, may help to confirm or refute this questions.

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DECLARATION OF INTEREST STATEMENT

The authors have no financial realationships, or conflits of interest to disclose.

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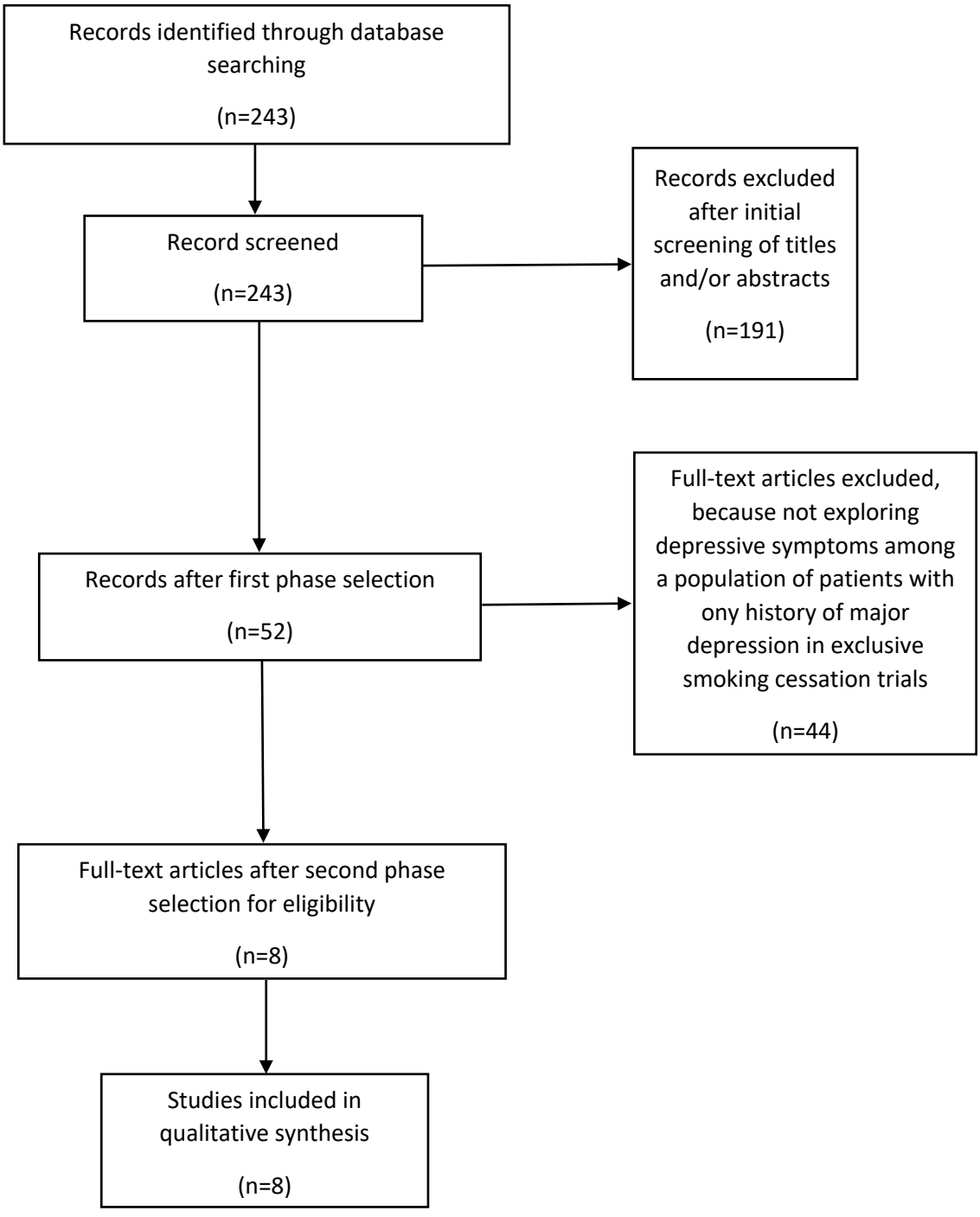
FIGURES

Fig. 1. Flowchart of Article Selection Process



Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. **- MANDATÓRIO**	Page 1: "The influence of smoking cessation on depressive symptoms in smokers with a history of major depression: a systematic review"
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Page 4: "The presence of depression increases the risk for smoking and vice versa, according that half of smokers seeking treatment have a history of depression. Depressive states can be provoked or exacerbated by smoking cessation and there is consistente evidence in that direction. It must be taken into account that smokers are not a homogeneous group so that it is important to develop different smoking cessation interventions for specific groups, such as people with past or current major depression. The aim of this review was to summarize the findings from published studies to reach a conclusion of which smoking cessation interventions are more efective in reducing depressive symptoms in this specific population and if smokers who successfully abstain are at risk of increased depressive symptomatology. A systematic review was conducted based on PRISMA´s guidelines. A bibliographic search was made by quering Cochrane and PubMed databases from which were included eight papers. The majority found improvement of depressive symptomatology in the subgroup of smokers who attained to stop smoking. Moreover, SSRI treatment was associated with a reduction of depressive symptoms, in particular sertraline that reached statistical significance in reducing depressive symptomatology when compared with placebo. Even though it is not possible to draw definitive conclusions, this review highlights some evidence that smoking cessation intervention may be a realistic opportunity to improve depressive symptomatology and that active intervention with SSRI may be a big aid in treatment."
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. **– MANDATÓRIO** ***O rationale corresponde à justificação da importância da revisão sistemática***	Page 4: "Scientific studies examining the influence of smoking cessation interventions on depressive symptoms in smokers with a history of major depressive disorder have been performed but no systematic review of this theme has been undertaken to date."
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). **- MANDATÓRIO**	Page 4: "(…)the aim of this study was to summarize the findings from published studies to reach a conclusion of which smoking cessation interventions are more effective in reducing depressive symptoms in this specific population and if smokers who successfully abstain are at risk of increased depressive symptomatology."
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. **– FACULTATIVO**	Not applicable, because a review protocol would not add information that is not already present in the manuscript.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. **– MANDATÓRIO** ***É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.***	Page 4 and 5: " (…) for publications that were related to smoking cessation and major depressive disorder. The only restriction was in terms of publication type: randomized controlled trials."
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. **– MANDATÓRIO** ***Em consonância com as boas práticas da***	Page 4: "The methodological approach used in this review was based in PRISMA`S guidelines, available at "prisma-statement.org". Two authors independently (PN & MB) conducted a search of PubMed and Cochrane´s databases (...)."

		Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov. ***Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.***	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. **– MANDATÓRIO** ***A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)***	Page 5: "The query used was: (Smoking cessation OR smoking cessations OR stopping smoking OR giving up smoking OR giving up smokings OR quitting smoking) AND (Major depressive disorder OR major depressive disorders OR involutional paraphrenia OR involutional paraphrenias OR involutional psychosis OR involutional psychoses OR involutional depression OR involutional melancholia)."
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). **– MANDATÓRIO** ***As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.***	Page 5: "In a first phase selection, repeated articles were sorted out, and the rest of articles were selected by title and abstract from the same query above. In a second phase, the selected articles were individually read and submitted to the following inclusion criteria: 1) population composed only of patients with major depressive disorder; 2) smoking cessation exclusive intervention; 3) depressive symptomatology as outcome. The articles in which the population had other psyquiatric diagnoses or other mood diseases that not major depression were excluded, as were publications in which the intervention was an healthy lifestyle promotion that includes but is not restricted to smoking cessation."
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. **– MANDATÓRIO** ***Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.***	Page 4: "". Two authors independently (PN & MB) conducted a search of PubMed and Cochrane´s databases for publications that were related to smoking cessation and major depressive disorder."
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. **– MANDATÓRIO** ***Trata-se de descrever as variáveis para as quais foi obtida informação.***	Page 5: "The data retrieved from each article included year of publication, country, methodology, population, type of smoking cessation interventions, criteria for classification of patients with MDD and to evaluate depressive symptoms, as well as key findings."
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. **– MANDATÓRIO** ***Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é***	Page 5: "The risk of bias was assessed by using "Revised Cochrane risk-of-bias tool for randomized trials"."

		altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Not applicable, since this systematic review was not accompanied by a meta-analysis.
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Not applicable, since this systematic review was not accompanied by a meta-analysis.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Not applicable, since this systematic review was not accompanied by a meta-analysis.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. **– MANDATÓRIO**	Page 5: "From the initial search, 243 articles were selected. After the first phase selection, 52 articles followed to the second phase selection, resulting in 8 final articles that were included in this review (Fig.1)."
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. **– MANDATÓRIO**	Page 5: "From all articles, 6 were from United States of America (USA), 1 from Europe (Netherlands) and 1 from USA and seven other european countries." "All the studies were related to smokers with current or past major depressive disorder (MDD). The majority of it (6) included only smokers with past MDD, no current. Another one included a population of stably treated current or past MDD. Other was circumscribed to smokers with current MDD." "Regarding classification of patients with MDD, the unanimously used instrument was Structured Clinical Interview for DSM disorders (SCID for DSM) (…)" "In terms of the scales used to assess evolution of depressive symptoms, four studies used Beck Depression Inventory (BDI) (…)" Page 6: "Firstly, the evolution of depressive symptoms over the time of the different studies was assessed without distinguishing types of interventions but comparing those who attained smoking abstinence with those who didn`t manage stop smoking." "Three studies approached the effect of treatment with SSRI compared with placebo in depressive symptomatology." "One study compared active nicotine patches with placebo patches (…)" "The other one study had varenicicline as NRT and placebo as control group." "The remaining studies consisted of non pharmacological strategies for smoking cessation."
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). **– MANDATÓRIO**	Page 7: "By using "Revised Cochrane risk-of-bias tool for randomized trials", two studies were classified as high risk of bias due to missing outcome data. (…) Four studies were classified as some concerns also due to missing outcome data. (…) Finally, two studies were classified as low risk of bias."
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Not applicable, since this systematic review was not accompanied by a meta-analysis.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. **– FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE**	Not applicable, since this systematic review was not accompanied by a meta-analysis.

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Not applicable, since this systematic review was not accompanied by a meta-analysis.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). **– MANDATÓRIO**	Page 7: "To begin with, the majority of studies found improvement of depressive symptomatology over time in the subgroup of smokers who stopped smoking during the study period (…)." Page 7 and 8: "The fact that similar interventions produced similar outcomes is a factor that allows to draw some conclusions. In this regard, SSRI treatment was associated with an improvement in depressive symptoms (Dalack et al., 1995; Glassman et al., 2001; Berlin et al., 2010), being that in two of the three studies SSRI, in particular sertraline, reached statistical significance in reducing depressive symptomatology when compared with placebo (Glassman et al., 2001; Berlin et al., 2010)."
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). **– MANDATÓRIO**	Page 9: "Some limitations need to be aknowledged. First, only two search engines were used so it is not known to what extent a significant quantity of relevant articles were left out. This systematic review only included eight papers. Second, some studies included a small number of participants, in particular two. However, in the concern of a lesser generability of findings the most relevant is that in all studies smokers were recruited through adds on social media, or other means but all interested in smoking cessation and somehow motivated to stop smoking. Furthermore, participants were excluded if concurrently taking antidepressive medication or current dystimia, or substance abuse other than tobacco, or even psychotic features and others. Only one studied included patients with current depression. Even though this restrictions aim to reduce confounding effect, it also contributes to the sample of participants not to be representative of the wider population. Moreover, this motivated patients belong to the mild or moderate spectrum of major depressive disorder in so that they represent a group more likely to be seen in a family practitioner´s than in a psychiatric´s office. Seen that, it is possible to argue that the influence of this smoking cessation trials in depressive symptoms may be generally overestimated. Studies that address the subset of smokers with severe major depressive disorder need to be developed. Another importante point is that MDD is a dichotomous variable and does not differentiate smokers with a single episode from those with multiple episodes of MDD and there may be relevant differences between this groups that require specific treatment. Relatively to studies that addressed non pharmacological treatments, interventions as controls were not the same but very similar in order that this studies were analyzed together."
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. **– MANDATÓRIO**	Page 9: "In conclusion, findings were consistent with other´s in literature that smoking cessation aids in psychiatric patients generally do not exacerbate psychiatric illness, in this particular case MDD. It is even possible to say that in a subset of mild to moderate patients with MDD motivated to quit smoking, smoking cessation may be a realistic opportunity to improve depressive symptomatology and that active intervention with SSRI may be a big aid in the treatment. A future systematic review, with more studies included and new scientific evidence, may help to confirm or refute this questions."
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Page 9: "None of the authors had any direct or indirect funding in support of this study."

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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