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The effect of smoking on the plasma concentration of tricyclic antidepressants: a systematic review

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Review Article

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Abstract

Smoking is highly prevalent in the psychiatric population, and hospital admittance usually results in partial or complete smoking cessation. Tobacco use is known to affect the metabolism of certain psychoactive drugs, but whether smoking influences the plasma concentration of tricyclic antidepressants (TCAs) remains unclear. This article investigates the possible effect of smoking on the plasma concentration of TCAs. A systematic review of the literature available on PubMed and EMBASE as of October 2020 was carried out using PRISMA guidelines. Studies reporting plasma concentrations of any TCA in both a smoking and a non-smoking group were included and compared. Ten eligible studies were identified and included. In the eight studies investigating the effect of smoking on amitriptyline and/or nortriptyline, five studies found no significant effect. Two studies investigating the effect of smoking on imipramine found a significant effect, and one study investigating the effect of smoking on doxepin found no significant effect. The majority of studies included in this review were influenced by small study populations and other methodical issues. The effect of smoking on the plasma concentration of TCAs is still not entirely clear. There is a possibility that smoking affects the distribution of TCA metabolites, but this is probably not of clinical importance.

Summations

- Smoking does not appear to have an overall effect on the plasma concentration of TCAs.
- Smoking may increase the demethylation of tertiary amine TCA to secondary amine TCA, but this is unlikely to be a clinical concern.

Considerations

- The majority of the reviewed studies suffered from the same methodological issues. This applies both to studies that found an effect of smoking and to those that did not. Therefore, the resulting evidence should be treated with caution.
- Only studies investigating the effect of smoking on the plasma concentration of amitriptyline, nortriptyline, imipramine and doxepin were identified. Therefore, it is not possible to establish the effect of smoking on other TCAs with certainty.
- Few studies investigating the subject were available, and more high-quality studies are needed to properly ascertain smoking's potential effect on the plasma level of TCAs.

Background

Cigarette smoking remains highly prevalent in European countries ranging from higher than 30% in central and eastern European countries to just under 20% in Nordic countries (World Health Organization - Regional Office for Europe, 2019). The prevalence of cigarette smoking has been shown to be even higher in patients with mental illnesses compared with the background population (Lasser et al., 2000; Poirier et al., 2002).

In addition to long-term health consequences, smoking is known to induce cytochrome P450 iso-enzymes which play a central role in drug metabolism. Specifically, polyaromatic hydrocarbons, which are a constituent of tobacco smoke, have been shown to induce CYP1A2 activity (Tantcheva-Poór et al., 1999; Kroon, 2007). In patients receiving drugs primarily metabolised by CYP1A2 such as clozapine, a drug with a narrow therapeutic index, abrupt smoking cessation can greatly increase plasma concentrations (Haslemo et al., 2006) with a risk of the patient

reaching toxic levels if not recognised and monitored properly. Many psychoactive drugs have established therapeutic windows, and deviation from these can either result in adverse or reduced effects of the drugs (Hiemke et al., 2018).

The metabolism of tricyclic antidepressants (TCAs) has also been suggested to be influenced by smoking (Desai et al., 2001; Taylor et al., 2018). As a rule, TCAs that are tertiary amines (e.g. amitriptyline, imipramine, doxepin) are demethylated to a secondary amine with similar pharmacological properties. However, the tertiary amines tend to be more potent inhibitors of serotonin reuptake, and the secondary amines tend to be more potent inhibitors of noradrenaline reuptake (Moraczewski & Aedma, 2021). In the case of amitriptyline, it is demethylated to nortriptyline primarily by CYP2C19 but also to a lesser extent by CYP1A2 among others (Olesen & Linnet, 1997). The same is true for doxepin which is demethylated to the active metabolite nordoxepin primarily by CYP2C19 with CYP1A2 and other CYP enzymes playing a minor role (Härtter et al., 2002). Imipramine is similarly demethylated to desipramine by CYP2C19, CYP3A4 and CYP1A2 (Shen, 1997).

In most cases, both the tertiary and secondary amines are then hydroxylated by CYP2D6 (Rudorfer & Potter, 1999). Amitriptyline is solely hydroxylated by CYP2D6 (Olesen & Linnet, 1997). Likewise, CYP2D6 is the main enzyme catalysing the hydroxylation of doxepin and its desmethyl metabolite nordoxepin (Kirchheiner et al., 2005). In the same pattern, imipramine and desipramine are both hydroxylated by CYP2D6 (Shen, 1997). The hydroxylation can be considered as the rate-limiting step in the elimination of TCAs, as it is needed before conjugation and ultimately renal excretion (Rudorfer & Potter, 1999). A schematic overview of the metabolism of TCAs is available in Fig. 1.

The hydroxy metabolites of TCAs appear to be pharmacologically active to some extent, but generally they are less potent than their parent compounds (Rudorfer & Potter, 1999). The clinical significance of the hydroxy metabolites is not entirely clear, but because they tend to have lower potency and are generally present in lower concentrations than their parent compounds (Ereshefsky et al., 1988), they appear to only play a minor role compared with the parent compounds.

TCAs belong to an old class of drugs, but they remain relevant in the clinical setting. A study using seven databases from five different countries showed that even though serotonin reuptake inhibitors (SSRIs) are the most prescribed antidepressant in four of the countries, TCAs are still heavily used, especially in Germany where they are prescribed twice as often as SSRIs (Abbing-Karahagopian et al., 2014). Even though these are widely used drugs, the connection between smoking and the effect on plasma concentration of TCAs has not yet been convincingly documented. Furthermore, it has been shown that TCA metabolism can be influenced by other factors such as age and sex, as it has been demonstrated that both elderly and females have higher plasma concentrations of TCAs than young and male subjects, respectively (Unterecker et al., 2013). Genetic polymorphisms of CYP2D6, a major enzyme involved in the metabolism of TCAs, can also result in an increased or decreased metabolism (Zhou, 2009). The CYP2D6-gene is highly polymorphic, and the resulting phenotypes are of interest when administering drugs metabolised by CYP2D6 such as TCAs. The ultra-rapid and poor metaboliser phenotypes are clinically important as dose adjustments can be needed. In most cases, therapeutic drug monitoring is recommended as well (Thuerauf & Lunkenheimer, 2006). The poor metaboliser phenotype is present in 7% of the Caucasian German population, whereas 3.5% of the Caucasian population has the ultra-rapid metaboliser phenotype (Thuerauf & Lunkenheimer, 2006). The recommended dose for poor metabolisers differs from TCA to TCA, but a reduction to 30%–60% of normal dose is advised depending on the specific TCA (Thuerauf & Lunkenheimer, 2006). There are less data on recommended doses for ultra-rapid metabolisers, but a greater than average dose is usually needed – nortriptyline being the most extreme with a recommended dose of up to 230% of normal dose (Thuerauf & Lunkenheimer, 2006). These figures imply that both poor and ultra-rapid metaboliser status have a great impact on the plasma concentration of TCAs.

All these different factors make establishing a connection between plasma concentrations of TCAs and smoking difficult and after an extensive search on PubMed and Embase, no previous systematic reviews investigating this connection were found. This article aims to contribute to the current field of knowledge on the effect of tobacco smoking on plasma concentrations of TCAs by analysing current literature and studies in a systematic review setting. The investigated population is patients receiving TCAs with smoking and non-smoking being the intervention and comparator, respectively.

The effect of smoking on the plasma concentrations of TCAs would especially be clinically relevant in patients treated with a TCA whose smoking behaviour changes – for example in the case of smoking cessation or an ex-smoker who starts smoking again.

If smoking truly has a clinically significant effect on the plasma concentration of TCAs, the clinical guidelines on the use of TCAs should be updated to reflect this.

Method

A literature search on PubMed and Embase was performed to find studies that investigate the association between smoking and the plasma concentration of TCAs in humans. Relatively broad inclusion criteria were used, as it was anticipated that there would not be a large number of relevant articles. All TCAs were considered, and a study population was eligible as long as it contained a smoking and a non-smoking subgroup. This includes healthy subjects as well as patients with major depressive disorder and other psychiatric or somatic diagnoses. Studies were included whether they used the same dosage for every patient or not and whether they adjusted the plasma concentration for dose or not. Studies were included that defined smoking status differently. No articles were excluded based on their year of publishing. The last database search was carried out on the 22nd of October 2020.

The reference sections of all identified relevant studies were searched manually in order to locate further relevant studies. The located studies were screened independently by the authors on title, abstract and/or full-text level using the Covidence tool for systematic reviews. Only articles written in English or Danish were considered. Case studies and reviews were excluded, but their reference lists were screened for relevant studies. A systematic review was carried out using PRISMA guidelines (Page et al., 2021).

Data on population size, age and sex of the population, distribution of smokers and non-smokers, TCA dose, plasma concentrations and p-values used for evaluation of significance levels were extracted from the included studies where these data were available.

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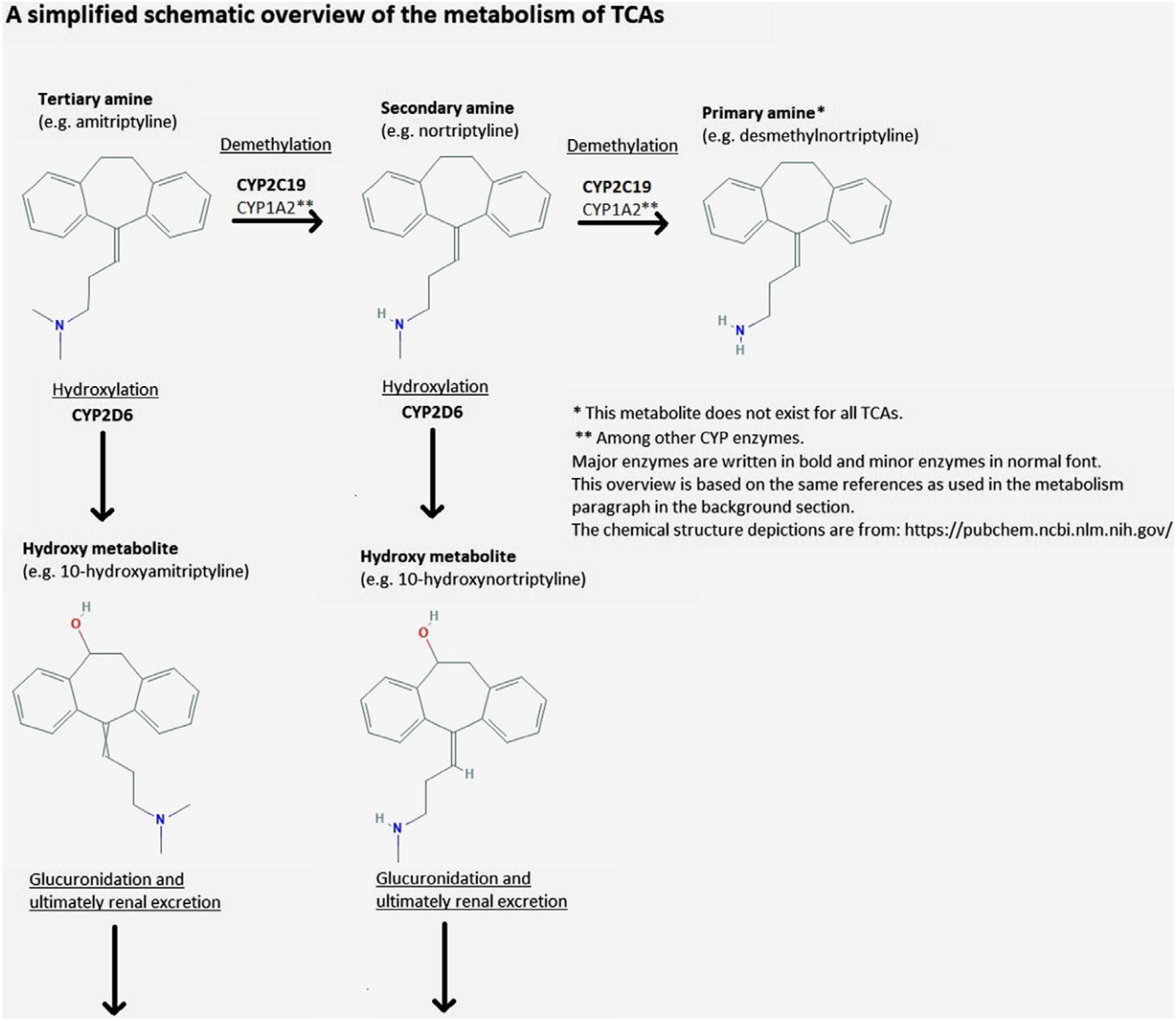

Fig. 1. A simplified schematic overview of the metabolism of TCA's.

Results

The flowchart that depicts the screening process is shown in Fig. 2. A total of 349 studies were imported for screening, and 43 studies were automatically removed because they were duplicates. Of the remaining 306 studies, 274 were deemed irrelevant based on the abstract. The remaining 32 studies were screened on full-text level. Of these, eight were excluded because they were partial reviews based on the data of older studies, six were excluded because they investigated a wrong outcome (often clinical response), three were excluded based on language (French or German), three studies did not present data on the plasma concentration of TCAs or did not use a non-smoking group for comparison. Two studies were unobtainable even after contacting university library resources and the editorial team of the journals directly. Finally, 10 relevant studies were identified and included in the systematic review.

The following describes the results of the included studies sorted by investigated drugs. The results are also shown in Table 1 along with demographic data where it was available.

Amitriptyline and nortriptyline

Eight studies investigating the potential effect of smoking on the plasma concentrations of either amitriptyline, nortriptyline or both were included in this review.

Alexanderson et al. (1969) included a total of 78 patients, who each received 0.2 mg nortriptyline per kg bodyweight daily. The study found no significant correlation between smoking and plasma concentration of nortriptyline ($p > 0.05$), but the mean plasma concentrations of the two groups were not reported and it is unknown whether the plasma concentrations were adjusted for dose.

Johnstone et al. (1981) measured the effect of smoking on the plasma concentrations of amitriptyline in 141 patients. Each patient received a daily dose of 150 mg amitriptyline. The study did not find a significant difference in the mean plasma concentration of amitriptyline between smokers and non-smokers (124.08 vs.142.89 ng/ml). No confidence intervals or *p*-value were presented for this conclusion, and the stated plasma concentrations were not dose adjusted.

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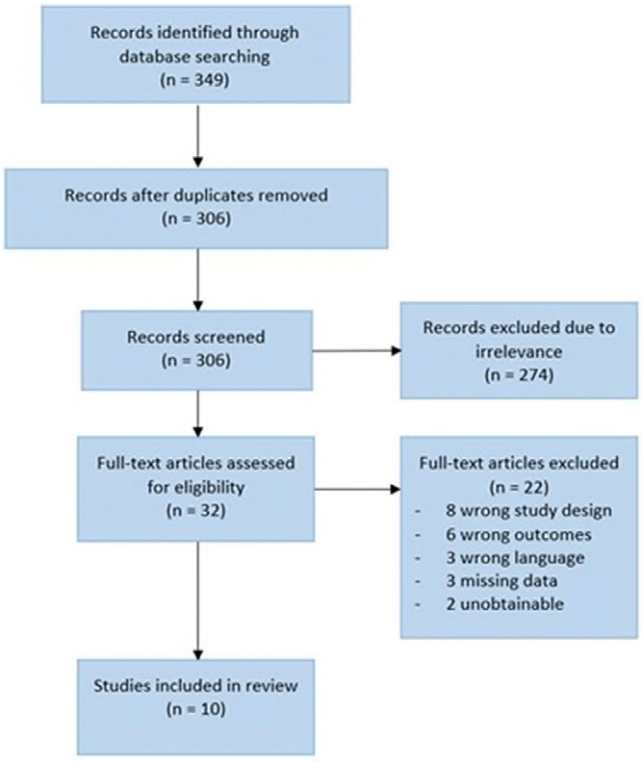

Fig. 2. Flowchart depicting the screening process of the included articles

Linnoila et al. (1981) investigated the plasma concentration of nortriptyline, and of amitriptyline and nortriptyline combined in 88 patients. Some patients received amitriptyline and others received nortriptyline both in greatly variable doses. The study showed that smokers had a significantly lower mean plasma concentration of nortriptyline than non-smokers (39.9 ± 18.5 vs. 69.4 ± 18.0 ng/ml, $p < 0.05$). The total concentration of amitriptyline and nortriptyline was also significantly lower in smokers than in non-smokers (73.4 ± 13.7 vs. 107.3 ± 31.5 ng/ml, $p < 0.05$). The stated plasma concentrations were not dose adjusted.

Norman et al. (1977) investigated the effects of smoking on plasma nortriptyline levels in a population of 53, who all received a daily dose of 150 mg nortriptyline. The study found no significant effect of smoking on the plasma levels of nortriptyline in smokers compared with non-smokers (191.2 ± 141.3 vs.169.3 ± 92.4 ng/ml, $p > 0.1$). The stated plasma concentrations were not dose adjusted.

Perry et al. (1986) investigated the plasma concentration of nortriptyline in a population of 24, who received different doses of nortriptyline. The study found a statistically significant lower nortriptyline plasma concentration in the smoking group compared with the non-smoking group (118 ± 33 vs. 158 ± 35 ng/ml, $p \leq 0.01$). The stated plasma concentrations were normalised to a daily dose of 100 mg nortriptyline.

Rickels et al. (1983) measured the plasma concentration of amitriptyline and nortriptyline in 74 patients treated with 150 mg amitriptyline daily. There was no significant correlation between smoking and the plasma concentration of amitriptyline and nortriptyline. Values for plasma concentration were not presented, and it is unknown whether the plasma concentrations were adjusted for dose.

Scherf-Clavel et al. (2019) studied 503 patients taking different doses of amitriptyline and found a statistically significant effect of smoking on the plasma concentration of amitriptyline with smokers having a lower plasma concentration than non-smokers (0.66 ± 0.46 vs. 0.83 ± 0.68 (ng/ml)/(mg/day), $p = 0.038$). The study did not, however, find a statistically significant effect of smoking on the nortriptyline plasma concentration ($p = 0.739$) nor on the combined plasma concentration of nortriptyline and amitriptyline ($p = 0.366$). All stated plasma concentrations were dose adjusted.

Thirty-eight investigated two population groups − one receiving amitriptyline ($n = 35$) and one receiving nortriptyline ($n = 30$) both in variable doses. The study did not find a significant difference in mean plasma concentrations between smokers and non-smokers taking amitriptyline (68.1 vs. 77.9 ng/ml). There was no difference in mean plasma concentrations between smokers and non-smokers taking nortriptyline either (95.7 vs. 86.3 ng/ml). The stated plasma concentrations were normalised to a daily dose of 1 mg amitriptyline or nortriptyline per kg body weight. No *p*-values were listed.

Five studies found no effect of smoking. The three studies that did find an effect of smoking found that smokers had a 20%−32% lower plasma concentration than non-smokers.

Imipramine

Two studies investigating the effect of smoking on imipramine plasma concentration levels were included:

Sutfin et al. (1988) had a study population of 14, who all received a daily dose of 200 mg imipramine. The conclusion was that smokers had a significantly lower total plasma concentration of imipramine, desipramine and their hydroxy metabolites 2-hydroxy-desipramine and 2-hydroxy-imipramine than non-smokers (mean 239 vs. mean 524 ng/ml, $p < 0.1$). The stated plasma concentrations were not dose adjusted.

Perel et al. (1975) included 22 patients, who received a daily dose of 3.5 mg imipramine per kg bodyweight. They found that the total desipramine and imipramine plasma concentrations were significantly lower in smokers compared with non-smokers (mean 160 vs. mean 290 ng/ml, $p < 0.05$). The stated plasma concentrations were not dose adjusted.

Both studies showed a lower plasma concentration of imipramine and its metabolites in smokers. The difference was 54% in Sutfin et al. and 45% in Perel et al. compared with non-smokers.

Doxepin

A single study by Scherf-Clavel et al. (2019) investigated the potential effect of smoking on the plasma concentration of doxepin. The study included 198 patients, who received different doses of doxepin. There was no significant effect of smoking on the plasma concentration of doxepin ($p = 0.861$) or its metabolite nordoxepin ($p = 0.358$) in smokers compared with non-smokers. The stated plasma concentrations were dose adjusted. No other studies investigating the potential effect of smoking on the plasma concentration of doxepin were found.

Discussion

The included studies are quite heterogeneous with regards to study population, TCA dosage and definition of smoking status.

With regards to smoking status, the studies had quite differently defined intervals determining whether study participants were allocated to the smoking group or the non-smoking group. The intervals ranged from one or more cigarettes per day (Johnstone et al.) to 15 or more cigarettes per day (Perel et al.) with three

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Table 1. The results and demographic data of the included studies

Included study	Drug measured	Population size	Smokers (S)	Non-smokers (NS)	Age, years	Sex	Dose	Mean plasma concentration (ng/ml)	Conclusion
Alexanderson et al. (1969)	Nortriptyline	$n = 78$	–[1]	–	45–51	–	0.2 mg/kg bodyweight/day	S: – NS: –	No effect, $p > 0.05$
Johnstone et al. (1981)	Amitriptyline	$n = 141$	$n = 67$	$n = 74$	–	–	150 mg/day	S: 124.08 NS: 142.89	No effect, p –
Linnoila et al. (1981)	Nortriptyline	$n = 40$	$n = 23$	$n = 17$	44.1 ± 12.6	F: 71% M: 29%	Ami: 117.1 ± 53.4 mg/day	S: 39.9 ± 18.5 NS: 69.4 ± 18.0	S lower conc., $p < 0.05$
	Amitriptyline + nortriptyline	$n = 35$	$n = 17$	$n = 18$			Nor: 10.13 ± 32.8 mg/day	S: 73.4 ± 13.7 NS: 107.3 ± 31.5	S lower conc., $p < 0.05$
Norman et al. (1977)	Nortriptyline	$n = 53$	$n = 22$	$n = 31$	42.3 ± 10.5	F: 42 M: 11	150 mg/day	S: 191.2 ± 141.3 NS: 169.3 ± 92.4	No effect, $p > 0.1$
Perel et al. (1975)	Imipramine + desipramine	$n = 22$	–	–	–	–	3.5 mg/kg bodyweight/day	S: 160 NS: 290	S lower conc., $p < 0.05$
Perry et al. (1986)[2]	Nortriptyline	$n = 24$	$n = 9$	$n = 15$	36 ± 13	F: 14 M: 10	50–150 mg/day	S: 118 ± 33 NS: 158 ± 35	S lower conc., $p < 0.01$
Rickels et al. (1983)	Amitriptyline + nortriptyline	$n = 74$	–	–	40.7 ± 13.3	F: 53 M: 21	150 mg/day	–	No effect, p –
Scherf-Clavel et al. (2019)[3]	Amitriptyline							S: 0.66 ± 0.46 NS: 0.83 ± 0.68	S lower conc., $p = 0.038$
	Amitriptyline + nortriptyline	$n = 503$	$n = 163$	$n = 340$	47.1 ± 12.3	F: 285 M: 218	10–300 mg/day	S: 1.36 ± 1.06 NS: 1.52 ± 1.21	No effect, $p = 0.366$[4]
	Doxepin	$n = 198$	$n = 62$	$n = 136$	49.8 ± 15.2	F: 106 M: 92	5–300 mg/day	S: 0.35 ± 0.50 NS: 0.43 ± 0.35	No effect, $p = 0.86$
Sutfin et al. (1988)	IMI + DMI + OH − DMI + OH − IMI[5]	$n = 14$	$n = 6$	$n = 8$	48.3	F: 12 M: 2	200 mg/day	S: 239 NS: 524	S lower conc., $p < 0.1$
38[6]	Amitriptyline	$n = 35$	$n = 18$	$n = 17$	<40:23 >40:12	F: 21 M: 14	5–200 mg/day	S: 68.1 NS: 77.9	No effect, p –
	Nortriptyline	$n = 30$	$n = 19$	$n = 11$	<40:24 >40:6	F: 18 M: 12		S: 95.7 NS: 86.3	No effect, p –

[1]– = data not presented in the study.
[2]Plasma concentrations normalised to a daily dose of 100 mg nortriptyline.
[3]Plasma concentrations of drugs listed as dose corrected plasma concentrations ((ng/ml)/(mg/day)), with p-values based on these as well.
[4]There was no significant effect on the plasma concentration of nortriptyline alone either, $p = 0.739$.
[5]Imipramine + desipramine + OH − desipramine + OH − imipramine.
[6]Plasma concentrations normalised to a daily dose of 1 mg amitriptyline or nortriptyline per kg body weight.

studies agreeing on a cut-off point of 10 or more cigarettes per day to define a person as a smoker. Four of the included studies did not include a defined interval determining whether study participants were categorised as smokers or not or they were missing data on the smoking frequency of their included population. These inconsistent intervals may prove problematic in the interpretation of the study results, as previous studies have shown that the number of cigarettes smoked per day influence the rate of CYP1A2 induction (Dobrinas et al., 2011), and that maximum induction might already be achieved after a daily consumption of 7–12 cigarettes (Haslemo et al., 2006). If a person smoking seven cigarettes daily has already achieved maximal induction but is still considered a non-smoker, the actual effect of smoking could be underestimated – especially if other enzymes involved in the metabolism of TCAs follow similar patterns of induction as CYP1A2. Furthermore, it has been described that self-reporting of smoking behaviour tends to be imprecise (Klesges et al., 1995) which might result in actual smokers being assigned to the non-smoking group in some of the studies. Such an inclusion of smokers in the non-smoking group would likewise result in an underestimation of the effect of smoking if any. Ultimately, an imprecise definition of smoking status and assignment to the wrong group could possibly lead to the conclusion that smoking does not have an effect on the plasma concentration of TCAs, even if smoking truly had an effect.

As stated previously in this article, gender itself can impact plasma concentration of TCAs with plasma concentration in females shown to be higher than in males (Hildebrandt et al., 2003; Unterecker et al., 2013). A demographic feature present throughout most of the included studies is that females are considerably more prevalent than males with variable ratios between the two sexes. Notably, not all studies list whether the gender distribution is the same among smokers and non-smokers which could have an important impact on the interpretation of the TCA plasma concentrations. Of the studies that did record the gender distribution among smokers and non-smokers (Perry et al., Norman et al., Scherf-Clavel et al., Sutfin et al.), Scherf-Clavel et al. find a significant effect of gender on amitriptyline and doxepin plasma levels. If the percentage of females present in the smoking and non-smoking groups is not quite similar, the impact of smoking on the plasma levels of TCAs could be over- or underestimated, and this could possibly influence the result.

The studies appear relatively homogeneous with regards to age, but not all list the age distribution in the smoking and non-smoking subgroups. Even though age, as previously stated, can affect the plasma concentration of TCAs with elderly having a higher plasma concentration due to decreased metabolism, the effect on the interpretation in this review is probably minimal.

Of the five studies that found a statistically significant effect of smoking on the plasma concentration of TCAs, a common denominator between them was that these were also the studies with the smallest study populations. The exception being Scherf-Clavel et al. who ascertained a connection between smoking and plasma concentration of amitriptyline with the largest study population included in this review ($n = 503$). The other four studies with significant results had populations of 35 or less – including the two imipramine studies that both showed a significant effect of smoking with populations of only 14 (Sutfin et al.) and 22 (Perel et al.). A small study population, as it is the case with these studies, leads to lower power of the study (Kirkwood & Sterne, 2010). Small population sizes could also falsely skew mean plasma concentrations, as one person with a very low or very high plasma concentration can have a huge impact leading to high standard deviations and possibly a wrong conclusion.

Consequently, the results of these four small studies cannot be considered conclusive due to the fact that they might be on the basis of coincidence and could have problems with reproducibility.

As it is also shown in Table 1, the studies included in this review were quite heterogeneous with regards to TCA dosage of the included population. Four of the studies used weight-dependent doses ranging from 0.2 (Alexanderson et al.) to 3.5 mg/kg/day (Perel et al.), whilst four other studies used a fixed dose on the entire population. Additionally, Scherf-Clavel et al. had doses of amitriptyline ranging from 10 to 300 mg/day with the use of dose corrected plasma levels in their interpretation. It has been thoroughly established that patients treated with TCAs have very different plasma concentrations even though they receive the same dose (Alexanderson et al., 1969). This is mainly due to inherently different metabolism and elimination of TCAs but could also be the result of various exogenic factors or co-administered drugs (Sjöqvist & Bertilsson, 1984). As a result of this, therapeutic drug monitoring is recommended for patients treated with TCAs to ensure that the patients are within the recommended therapeutic range of the drug (Gram et al., 1984). With regards to this review, the use of equivalent doses or dose corrected plasma concentrations is necessary in order to be able to compare the group of smokers and non-smokers. Only Linnoila et al. does not use either of these methods for dosage, which makes it impossible to interpret if smoking truly has an effect on the plasma concentration as they claim. A reasonable approach to dosage does, however, by no means guarantee that a found difference is truly due to smoking. A lower plasma concentration in smokers than in non-smokers is not necessarily the effect of smoking but could just as well be on the basis of interindividual variability in metabolism. This must be considered in the interpretation of the results. Important information on the interindividual differences in metabolism of the participants is not investigated in any of the studies – for example the CYP2D6 genotype of the participants. In fairness, genotype testing was most likely not technically possible in the older studies and probably not economically feasible in the large study by Scherf-Clavel et al.

As described in the background section, CYP1A2 is one of the minor enzymes that catalyse the demethylation of tertiary amines to secondary amines. CYP1A2 is induced by smoking, so theoretically the demethylation of the tertiary amine to the secondary amine could be increased in smokers with a corresponding lower concentration of the tertiary amine and higher concentration of the secondary amine in a smoking patient compared with a non-smoking one. Interestingly, Scherf-Clavel et al. found that smokers have a significantly lower mean dose corrected plasma concentration of amitriptyline than non-smokers (0.66 ± 0.46) vs. (0.83 ± 0.68 (ng/ml)/(mg/day)). This supports the notion that smoking increases demethylation via CYP1A2 in a non-negligible way. However, the interindividual variability in plasma concentrations in the study is considered as illustrated by the large standard deviations. Equally importantly, the study does not find that smokers have a significantly higher concentration of nortriptyline, and the actual effect of smoking on demethylation appears minor at best.

Perry et al. found that smokers taking nortriptyline had a lower plasma concentration of nortriptyline than non-smokers. Several secondary amine TCAs can be demethylated further to a primary amine metabolite – in the case of nortriptyline, it can be demethylated to desmethylnortriptyline by CYP1A2 among

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others (Thorn, n.d.). Sparse literature on desmethylnortriptyline is available, but one animal study found desmethylnortriptyline to have pharmacological activity quite similar to amitriptyline and nortriptyline (Hyttel et al., 1980). Theoretically, this could in part explain the findings of Perry et al., as this metabolite was not measured. However, as seen in Table 1, the sample size of the study is small, the standard deviations of the mean concentrations are relatively large, and the difference in mean plasma concentrations is modest (25%). The found difference between smokers and non-smokers is most likely due to the great interindividual variability in plasma concentrations of TCAs or perhaps due to a CYP2D6 ultra-rapid metaboliser in the smoking group or a poor metaboliser in the non-smoking group. It seems much less likely that the found difference is due to a metabolic shift from nortriptyline to desmethylnortriptyline via CYP1A2. If smoking does increase the demethylation of nortriptyline to desmethylnortriptyline in significant quantities, it is probably not clinically relevant as the sparse data available on desmethylnortriptyline indicate that this metabolite has similar pharmacological properties to those of its parent compound.

As described in the background section and shown in Fig. 1, the two main routes of metabolism that a TCA can undergo are demethylation and hydroxylation. As discussed above, smoking does not appear to influence the demethylation of TCAs in a clinically significant way. Smoking induces CYP1A2, which demethylates tertiary amine TCAs to secondary amine TCAs resulting in an increased secondary amine to tertiary amine ratio compared with the ratio in a non-smoker. However, as the resulting metabolite has similar pharmacological properties to its parent compound, this potential metabolic shift is without clinical significance. Therefore, if smoking were to have a clinically relevant effect on the plasma concentration of TCAs, it must have an effect on the hydroxylation via CYP2D6 and thereby lower the total concentration of both tertiary and secondary amines. Only 3 of the 10 studies find that smokers have a lower concentration of tertiary and secondary amines combined – Linnoila et al., Perel et al. and Sutfin et al. These three studies have very small sample sizes and as discussed above it can therefore not be ruled out that their findings are the result of coincidence. Also discussed earlier, Linnoila et al. does not use an optimal dosage strategy which makes their results difficult to interpret. The found differences are most likely due to the well-known great variability in plasma concentrations between individuals treated with TCAs. The results of these three studies could suggest that smoking increases the hydroxylation of TCAs. However, because of the above-mentioned shortcomings of the studies, and because the largest study by far (Scherf-Clavel et al.) cannot reproduce this effect on the combined concentration of the tertiary and secondary amines, it is not deemed as credible evidence that smoking increases the hydroxylation of TCAs via CYP2D6.

Perhaps, the most important of the included studies is the one by Scherf-Clavel et al. as it is by far the largest of the included studies with 503 patients in the amitriptyline/nortriptyline group. Another strength is that they also present the distribution of women in the smoking and non-smoking group, and the percentage of women in the two groups are quite similar, which as discussed earlier, is important in order to compare the two groups. Scherf-Clavel et al. also use dose-adjusted plasma concentrations, which is paramount when comparing subjects receiving different doses. They find that smokers have a lower concentration of amitriptyline than non-smokers, and they demonstrate an increased nortriptyline to amitriptyline ratio in smokers, but they do not find an effect on the combined plasma concentration of amitriptyline and nortriptyline. This is also what would be expected from a pharmacological point of view, as amitriptyline is demethylated to nortriptyline by among others CYP1A2 – an enzyme induced by smoking. With increased demethylation via CYP1A2, one would expect smokers to have an increased ratio of nortriptyline to amitriptyline but the same total plasma concentration of amitriptyline and nortriptyline, because hydroxylation via CYP2D6 is the rate-limiting step in the elimination of TCAs and tobacco smoke is not a known inducer of CYP2D6.

Most of the included studies do not measure the concentration of hydroxy metabolites, and this appears to be a reasonable approach, as the hydroxy metabolites of TCAs in general are less potent and are present in lower concentrations than their parent compounds as described in the background section. As only studies investigating the effect of smoking on the plasma concentration of amitriptyline/nortriptyline, imipramine/desipramine and doxepin were found, it is difficult to assess the effect of smoking on other TCAs with certainty. However, as the principal routes of metabolism and the main enzymes catalysing these reactions are the same for other TCAs (Rudorfer & Potter, 1999), it also appears unlikely that smoking has a clinically significant effect on the plasma concentration of other TCAs not discussed in this study.

Conclusion

As this review has demonstrated, the evidence of whether smoking has an effect on the plasma concentration of TCAs is not entirely clear with only a few studies available investigating the connection. Furthermore, several of these studies suffered from different issues such as small study populations, inadequate defined smoking status, inappropriate TCA dosage strategy and limited information with regards to other factors influencing the metabolism of TCAs.

If smoking has an effect on the plasma concentration of TCAs, it could be on the distribution of the different TCA metabolites.

This effect would be increased demethylation through induction of CYP1A2, but to the clinician this is most likely irrelevant. The reviewed studies do not provide credible evidence that smoking increases hydroxylation via CYP2D6. Additional studies that take the earlier mentioned issues into account would have to be conducted to investigate this effect further. Based on the currently available evidence, which admittedly is sparse, smoking does not appear to have a clinically significant effect on the plasma concentration of TCAs.

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