BJPsych Open (2023)
9, e53, 1–9. doi: 10.1192/bjo.2023.15

Dry mouth effects from drugs used for depression, anxiety, schizophrenia and bipolar mood disorder in adults: systematic review

Cherilyn Xue Wei Teoh, Millie Thng, Serene Lau, Meng-Wong Taing, Sarah Y. Chaw, Dan Siskind and Steve Kisely

Background

Poor oral health is increasingly recognised as an important comorbidity in people with psychiatric illness. One risk factor is psychotropic-induced dry mouth.

Aims

To perform a systematic review of the severity of dry mouth due to psychotropic drugs in adults (CRD42021239725). Study quality was assessed using the Cochrane risk of bias tool.

Method

We searched the following databases: PubMed, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, CINAHL and Web of Science. We included randomised controlled trials (RCTs) measuring the severity of drug-induced hyposalivation and xerostomia.

Results

Eighteen RCTs with 605 participants were included. Severity of drug-induced dry mouth was compared among eight drug classes and/or against placebo. All studies were published 20 to 40 years ago and included tricyclic antidepressants (TCAs), serotonin specific reuptake inhibitors (SSRIs) and other drug classes. Meta-analysis was not feasible owing to design heterogeneity. TCAs caused more severe dry mouth, both objectively and subjectively, than placebo or other drug classes. SSRIs were generally associated with less severe symptoms. However, there was no information on antipsychotics or more recently available antidepressants, and there was minimal information on mood stabilisers. Most studies were on healthy subjects, limiting the generalisability of findings. Only one study measured both objective and subjective dry mouth, which have different clinical implications.

Conclusions

Psychotropic-induced dry mouth is a poorly researched area, and well-designed RCTs of newer psychotropic drugs using standardised objective and subjective measures are indicated. Given the ongoing use of TCAs for treatment-resistant depression, prescribers need to remain vigilant for xerostomia.

Keywords

Dry mouth; xerostomia; hyposalivation; psychotropic drugs; psychiatric illness.

Dry mouth can present as a sign (salivary gland hypofunction), symptom (xerostomia) or both.[1] Salivary gland hypofunction is diagnosed based on objective measures of decreased saliva production, whereas xerostomia is the subjective experience of oral dryness and is based on self-report.

In dentistry, dry mouth is an area of interest because of its negative effects on oral health, which include increased risks of dental caries, periodontal disease, tooth demineralisation, tooth sensitivity and oral candidosis.[1,2] It can also lead to dysgeusia, dysphagia and difficulties with speech and mastication.[3]

Psychotropic medications and xerostomia

Psychotropic medications are among the many causes of dry mouth.[1,3] The importance of the issue was highlighted in recent reviews of the oral health side-effects of psychotropics reported to drug companies such as the Monthly Index of Medical Specialties (eMIMs).[4] Of the 57 identified drugs (23 antidepressants, 22 antipsychotics or mood stabilisers, and 12 anxiolytic or sedative medications), xerostomia was the most frequently reported side-effect (91%) of the 28 identified oral symptoms among all classes of medication.[4]

Xerostomia can occur through several mechanisms but is often secondary to the anticholinergic effect arising from deactivation of the M3 muscarinic receptor, leading to poorer oral health outcomes.[5–12] This is a significant problem given the range of agents and frequency of psychotropic prescription.[13,14]

The current study

The existing literature on drug-induced dry mouth investigates the risk within a specific population or drug class but does not address severity. For instance, there are studies that investigate dry mouth in older people,[3,5,6] but these may overestimate the effects of drug-induced dry mouth in the general population, as salivary production reduces with age. This is an important gap to address because psychiatric illnesses often start in early adulthood, exposing patients to decades of dry mouth.[15] Other work has assessed the risk of dry mouth in working-age adults but was restricted to a limited range of psychotropics and did not consider severity.[7–10,16–20]

We therefore assessed the severity of both subjective and objective dry mouth secondary to psychotropic drugs in adults above 17 years old among eight drug classes and/or against placebo.

Methodology

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta Analyses and preregistered the

https://doi.org/10.1192/bjo.2023.15 Published online by Cambridge University Press

study with PROSPERO (CRD42021239725). As this was a systematic review of the published literature, ethical approval and written informed consent were not needed.

Search strategy

A systematic search for studies was conducted using the following databases: PubMed, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials, CINAHL and Web of Science. We used medical subject headings, Emtree terms, titles and keywords related to dry mouth, antidepressants, antianxiety agents, antipsychotics, mood stabilisers and study design. The full search strategy can be found in Supplementary Table 1 available at https://doi.org/10.1192/bjo.2023.15. No publication date or language filters were applied to the searches.

Drugs used for each mental health condition were cross-checked with Martindale[21] and Cockburn et al[4] based on data from the Australian Medicines Handbook, Australian Therapeutic Guidelines, eMIMs and UpToDate databases. This provided a comprehensive list of drugs to include in the search terms, ensuring that all potentially relevant papers were searched.

Selection process

Duplications were eliminated using Endnote, and articles were independently evaluated by pairs of reviewers (C.X.W.T., M.T. or S.L.) based on title and abstract. All full-text articles were independently assessed by two reviewers to be 'included', 'excluded' or 'maybe'. Any discrepancies were resolved by consulting a third reviewer.

Eligibility criteria

We included all randomised controlled trials (RCTs) in both in-patient and out-patient settings of drug-induced dry mouth, including xerostomia and hyposalivation, as primary outcome. Severity could be assessed subjectively by questionnaire or objectively through stimulated and unstimulated salivary flow rate, oral mucosal wetness or oral moisture meter. Studies could investigate multiple drugs, specific drugs or drug classes. Comparisons included placebo, usual treatment or another intervention.

We excluded observational studies (such as case–control, cohort and cross-sectional designs), as well as those on burning mouth syndrome (BMS).[22] Although BMS is commonly associated with dry mouth, it is difficult to establish whether dry mouth is a result of drug use or BMS. Observational studies may not adequately control confounding between comparisons and hence were excluded.

Data collection process

Data extraction was conducted by four authors (C.X.W.T., M.T., S.L. and S.K.) with at least two independently collecting data from each study. A further author was available to resolve or check any differences between raters. This exceeded the original PROSPERO protocol, which states that one author's data extraction should only be checked by another for accuracy. Tables of included studies reported on the objective or subjective measures of dry mouth and the associated drugs. Drugs had head-to-head comparisons with other active agents, or indirect comparisons against placebo or both. Other information included each study's author and publication date, out-patient or in-patient setting, age, gender and diagnosis of subjects. We planned to meta-analyse any comparisons where there were more than two studies with sufficient uniformity of method and outcomes.

Risk of bias

Chosen papers were judged for quality using the Cochrane risk of bias tool.[23] Papers were scored as being of low, high or unclear risk of bias by two independent reviewers.

Results

The initial search identified 5199 references (Fig. 1). After duplicates had been removed, 1634 remained and, following screening at title, abstract and full-text levels, 18 studies were included (Fig. 1).[24–41] Where stated, all were in out-patient settings. Fourteen studies were conducted in healthy subjects and four in people with depression (Tables 1 and 2). The majority of the studies in healthy subjects were of single doses

Outcomes

Of the included studies, 14 focused on objective measures of hyposalivation (Table 1), three investigated subjective measures of xerostomia severity (Table 2) and one investigated both objective and subjective measures of severity (Tables 1 and 2).[36]

Objective measures used one of two validated techniques that have been shown to give similar results (Table 1).[42–47] Two studies used the stimulated spit method.[30,41] This is where saliva is collected in a funnel following the sucking of a lozenge.[44] The others measured spontaneous saliva flow using cotton rolls. In this method, absorbent material is placed in the mouth for a fixed time (usually 2 min), and the increase in weight is compared at intervals pre- and post-dose.[45–47] Numerical values were therefore estimated using WebPlotDigitizer online software.[48] In terms of subjective data, two studies used visual analogue scales, and the other two used three- or four-point rating measures (Table 2).

Differences by drug class

Tables 1 and 3 summarise the results by drug class. Tricyclic antidepressants (TCAs) were the most commonly studied class and were included in all the studies, either as the agent of interest or the comparison drug ($k = 18$).[24–41] These were followed by selective serotonin reuptake inhibitors (SSRIs, $k = 5$)[28,29,34,36,38] and tetracyclic antidepressants (TeCAs, $k = 6$).[28,31,32,38,39,41] The remaining studies were on monoamine oxidase inhibitors (MAOIs, $k = 2$),[28, 38] norepinephrine–dopamine reuptake inhibitors (NDRIs, $k = 2$),[28,38] serotonin antagonist and reuptake inhibitors ($k = 2$),[26,35] lithium citrate ($k = 2$)[28,38] and reboxetine, a norepinephrine reuptake inhibitor (NRI) ($k = 1$).[36]

In general, TCAs caused more severe dry mouth on both objective and subjective measures in comparison with placebo and other drug classes. Amitriptyline was the most studied TCA, and all 12 studies found that it caused more severe dry mouth than placebo and all active agents on both objective and subjective measures. Comparing within the drug class, doxepin caused more severe dry mouth than desipramine.[24,37] When compared with placebo, there were mixed findings for desipramine, with it causing more severe dry mouth than placebo in two studies but the same as placebo in another.[24,37,40]

In terms of TeCAs, both mianserin and oxaprotiline caused less severe dry mouth than amitriptyline on objective measures in two studies,[39,41] although mianserin had similar effects to other TCAs in two others.[28,38] It caused less severe dry mouth than nortriptyline subjectively in a further study.[32] There were no comparisons within the drug class. When compared with placebo, TeCAs caused more severe dry mouth than placebo,[28,31,38] as well as lithium citrate and isocarboxazide.[38]

https://doi.org/10.1192/bjo.2023.15 Published online by Cambridge University Press

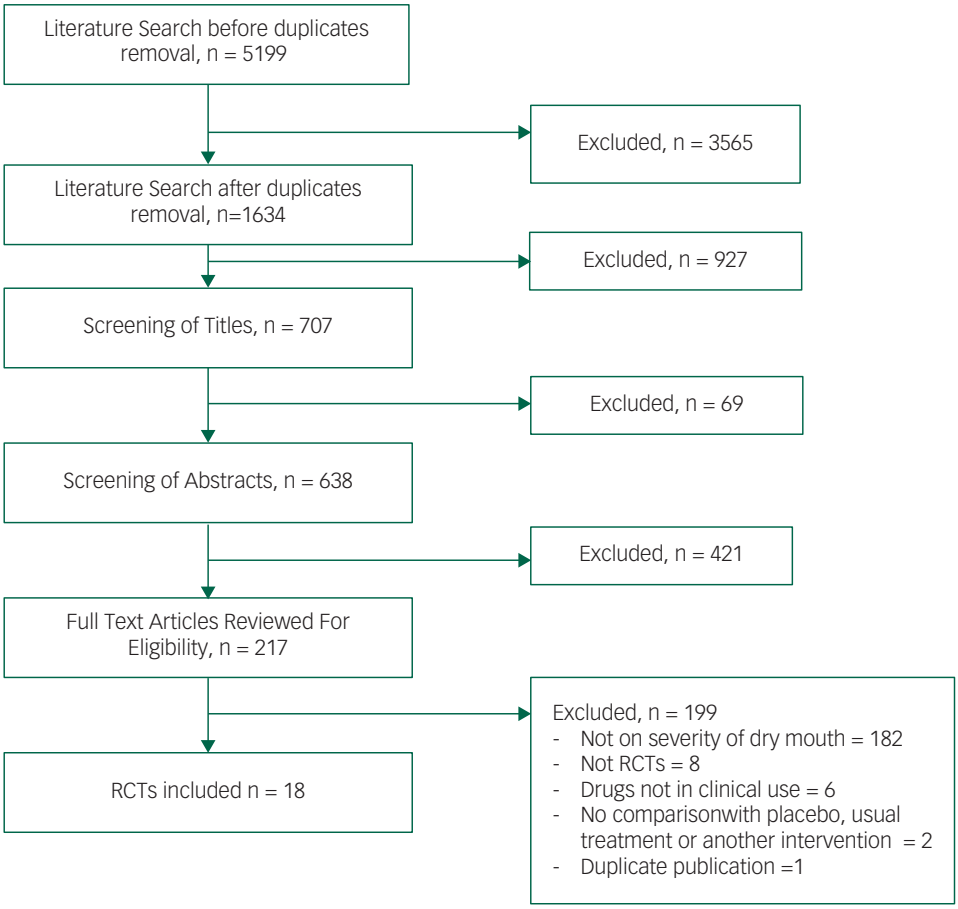

Fig. 1 Flow diagram.

There was less data on other drug classes. For SSRIs, fluvoxamine was the same as placebo in one study,[29] as was citalopram in another.[36] However, citalopram caused more severe dry mouth than placebo on subjective measures in a third study.[34] MAOI isocarboxazide, NRI reboxetine and mood stabiliser lithium citrate were the same as placebo,[28,36,38] whereas NDRI nomifensine caused significantly more severe dry mouth than placebo in one study,[38] but less severe symptoms than imipramine, nortriptyline and mianserin in two papers.[28,38]

Risk of bias

Table 4 shows the risk of bias ratings. Eight out of 18 studies reported on methods to blind participants and assessors such as making placebo and intervention pills identical in appearance. A similar proportion had low attrition rates. However, the remaining domains were rated as unclear or at high risk of bias. Owing to the age of the studies (1972–2001), none used reporting guidelines such as CONSORT.

Discussion

To our knowledge, this is the first systematic review of both the objective and subjective severity of dry mouth associated with psychotropic medications, as previous reviews only assessed self-reported prevalence without considering severity.[3,7,9] We found that in both direct comparisons between drugs and indirect comparisons between drugs and placebo, newer psychotropic agents such as SSRIs caused less dry mouth objectively and subjectively. By contrast, TCAs (especially amitriptyline) were generally associated with a greater severity of dry mouth largely owing to their anticholinergic effects. This finding extends existing literature, including a previous meta-analysis that was restricted to the self-reported prevalence, not severity, of dry mouth in individuals receiving SSRIs.[9,49]

Despite the scope of the review being extended to a range of psychotropic drugs, concerns included the relatively low number of included studies and their age; all were over 20 years old. In particular, there was no information on many commonly used psychotropics including fluoxetine, sertraline, duloxetine, venlafaxine and desvenlafaxine. This is despite xerostomia being identified as by far the most frequently reported symptom of 28 drug-company-reported oral side-effects among all classes of psychotropic medications.[4] For instance, xerostomia has been reported as a common side-effect (>10%) of the following newer and commonly used antidepressants: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, desvenlafaxine and duloxetine.[4] These were generally the same medications for which we could not find any literature on the severity of dry mouth when it does occur.

Of particular concern is that despite the potential oral health consequence of drug-induced dry mouth, many people do not access dental care. In a nationwide study of Australian service veterans, 40% ($n = 50\,679$) were taking at least one medication that caused dry mouth, but fewer than half of them made a claim for dental services in the following year.[50]

Limitations

This work had several limitations. Given that the studies were published between 20 and 40 years ago, most investigated medications

https://doi.org/10.1192/bjo.2023.15 Published online by Cambridge University Press

https://doi.org/10.1192/bjo.2023.15 Published online by Cambridge University Press

Table 1 Included studies measuring objective dry mouth

	Study	Place	Setting	*N*	Age, years	Male, %	Diagnosis	Outcome measure	Comparison group	Score	Intervention	Score	*P*-value
1	Arnold, 1981	USA	Out-patient	10	18–20	100	Healthy subjects	Mean change in weight (g) of three cotton rolls (two buccally and 1 sublingually) on five occasions 2 min apart pre- and post-treatment	Placebo	0.95 g[a]	Amitriptyline Doxepin Desipramine	0.68 g 0.63 g 1.00 g	F-test <0.05[a]
2	Ghose, 1987	Wales	Out-patient	6	65–72	50	Healthy subjects	Stimulated mean salivary volume (mL) per 2 min collected through the spit method into a filter tunnel	Placebo	9.60 mL [a]	Amitriptyline Lofepramine	6.92 mL 9.50 mL	<0.05[a] NS[a]
3	Guimarães, 1987	Brazil	Out-patient	40	19–34	42.5	Healthy subjects	Mean change in weight (g) of three cotton rolls (two buccally and one sublingually) after 2 min exposure pre- and post-treatment	Placebo	Not stated	Chlorimipramine Maprotiline	Not stated	F-test <0.01[a]
4	Longmore, 1988	UK	Unknown	8	18–30	100	Healthy subjects	Mean (%) change in three pre-weighed cotton rolls (g) from three measurements	Placebo	+14%	Amitriptyline Conventional trazodone Controlled-release trazodone	–40% –22% –19%	<0.05[b] NS NS
5	Peterson, 1978	USA	Unknown	10	20–25	0	Healthy subjects	Mean (%) change in weight of cotton roll repeated five times at 2 min intervals	Placebo	–1.87%	Desipramine Doxepin	–44.9% –64.2%	<0.05[b,c]
6	*Rafaelsen, 1981*	Denmark	Unknown	21	19–41	66.7	Healthy subjects	Spontaneous whole saliva and parotid secretion as measured by mean increase in pre-weighed cotton roll (g); 2 min each, two buccally for whole mouth; four buccally for parotid	Session 1 Placebo Lithium Isocarboxazide Session 2 Placebo	 0.779 g 0.807 g 0.757 g 0.935 g	Session 1[d,e] Nomifensine Zimelidine Imipramine oxide Nortriptyline Mianserin Session 2[d] Maprotiline Clomipramine Amitriptyline Imipramine	 0.629 g 0.618 g 0.479 g 0.329 g 0.413 g 0.417 g 0.328 g 2.260 g 0.310 g	 F-test <0.05[d] F-test <0.05[d]
7	*Szabadi, 1980*	UK	Out-patient	8	19–30	25	Healthy subjects	Mean (%) change in three pre-weighed cotton rolls (g) from three measurements	Placebo	10%	Amitriptyline Desipramine	–69% –36%	<0.000[a] 0.01[a]
8	Blackwell, 1972	USA	Out-patient	6	22–30	50	Healthy subjects	Mean percentage change in weight of three cotton rolls (two buccally and one sublingually on five occasions 2 min apart pre- and post-treatment	Placebo	21.56%	Dimethacrin Imipramine	6.28% –73.96%	NS[f] <0.05[f]
9	*Bourne, 1993*	UK	Out-patient	10	18–45	100	Healthy subjects	Mean change in weight (g) of three cotton rolls (two buccally and one sublingually) on five occasions 2 min apart pre- and post-treatment	Placebo	0.22 g	Amitriptyline Amoxapine	–0.43 g 0.06 g	<0.05[a] NS
10	*Clemmesen 1984*	Denmark	Out-patient	11	19–41	54.5	Healthy subjects	Mean (%) difference from placebo in weight of three cotton rolls (two buccally and one sublingually) on five occasions 2 min apart pre- and post-treatment	Placebo	Reference	Nortriptyline Imipramine Mianserin Isocarboxazide Lithium citrate Nomifensine Zimelidine	–54.5% –36.5% –37.9% –12.8% –13.9% –25.3% –23.3%	<0.01[d] <0.05[d] <0.01[d] NS[d] NS[d] NS[d] NS[d]
11	*Flett, 1992*	UK	Unknown	10	19–25	100	Healthy subjects	Mean change in weight (g) of three cotton rolls (two buccally and one sublingually) on three occasions 5 min apart pre- and post-treatment	Placebo	–0.01 g	Amitriptyline Fluvoxamine	–0.21 g –0.05 g	<0.05[a] NS
12	Jang, 1991	South Korea	Unknown	17	Mean: 24.6	100	Healthy subjects	Mean (%) change in weight of three cotton rolls (two buccally and one sublingually) on two occasions 3 min apart pre- and post-treatment	Placebo	Not stated	Nortriptyline	–51.9%	<0.05

13	*Penttila, 2001*	Finland	Unknown	8	18–27	100	Healthy subjects	Objective: percentage change in weight of three cotton rolls pre- and post-treatment	Placebo	Not stated	Amitriptyline Reboxetine Citalopram	–47% –38% Not stated	0.027[a] NS[a] NS[a]
14	Roffman, 1983	USA	Out-patient	308	–	57	Depression	Percentage change in weight of cotton rolls pre- and post-treatment	Placebo	No change	Amitriptyline Oxaprotiline	–63% –40%	<0.05[g]
15	*Ghose 1976*	UK	Out-patient	17	–	–	Depression	Stimulated mean salivary volume (mL) collected on three occasions through the spit method into a filter tunnel	Mianserin	6.96 mL	Amitriptyline	4.49 mL	0.02[a]

a. 2–4 h post-dose.
b. 5–6 h post-dose.
c. Both agents significantly worse than placebo, doxepin significantly worse than desipramine.
d. 10 h post-dose for whole-mouth results only.
e. Within the group, nomifensine and zimelidine inhibited salivation significantly less than imipramine and mianserin.
f. Up to 72 h post-dose.
g. After 5 weeks of therapy compared with placebo. However, amitriptyline was significantly worse than oxaprotiline.
TCA, tricyclic antidepressants; NS, non-significant. Data presented for highest dose of each agent. Studies marked in italics indicate where results were only presented in graphical form.

Table 2 Included studies measuring subjective dry mouth

	Study	Place	Setting	*N*	Age, years	Male, %	Diagnosis	Comparison group	Intervention	Outcome measure
1	Lader, 1986	–	Out-patient	12	18–40	Study A:100 Study B: 50	Healthy subjects	Amitriptyline Placebo	Citalopram	Worse dryness of the mouth on amitriptyline compared with citalopram and placebo on VAS side-effects scale rated from 0 to 100 ($P < 0.001$)
2	Penttila, 2001	Finland	Unknown	8	18–27	100	Healthy subjects	Placebo	Amitriptyline Citalopram Reboxetine	No difference in sensation of dryness of mouth using VAS rated from 0 to 100 up to 6 h post-dose
3	Botros, 1989	–	In-patient and out-patient	17	18–80	–	Depression	Amitriptyline	Trazodone	Frequency and severity measured on a three-point scale, worse on amitriptyline at 20 day follow-up ($P < 0.001$)
4	Hoc, 1982	Belgium	Out-patient	86	26–70	38.4	Depression	Nortriptyline	Mianserin	Worse for nortriptyline on four-point side-effect scale up to 6 week follow-up ($P < 0.001$)

VAS, Visual Analogue Scale.

Table 3 Summary of comparisons

Drug class	Drug name	*K*	Findings
Tricyclic antidepressants (*k* = 18)	Amitriptyline	12	Objective and subjective measures showed that drug caused more severe dry mouth than placebo and all active agents (desipramine, doxepin, lofepramine, trazodone, nomifensine, zimelidine, nortriptyline, mianserin, amoxapine, fluvoxamine, reboxetine, citalopram, oxaprotiline) in all 12 articles including one moderately large study (*n* = 308).
	Nortriptyline	4	Objective measures showed that drug caused more severe dry mouth than placebo in three small studies. Subjective measures showed that drug caused more severe dry mouth than mianserin in one larger study (*n* = 86).
	Desipramine	3	Objective measures showed that drug caused more severe dry mouth than placebo but less than doxepin and amitriptyline in two small studies. Objective measure showed that drug was the same as placebo in another small study.
	Doxepin	2	Objective measures showed that drug caused more severe dry mouth than placebo and desipramine in two small studies.
	Imipramine	3	Objective measures showed that the drug caused more severe dry mouth than placebo in three small studies, as well as lithium and isocarboxazide in one small study
	Amoxapine	1	Objective measure showed that drug was the same as placebo in one small study.
	Clomipramine/chlorimipramine	2	Objective measures showed that drug caused more severe dry mouth than placebo but was the same as maprotiline in two small studies.
	Dimethacrin	1	Objective measure showed that drug was the same as placebo in one small study.
	Lofepramine	1	Objective measure showed that drug was the same as placebo in one small study.
Selective serotonin reuptake inhibitors (*k* = 5)	Citalopram	2	Objective and subjective measures showed that drug was the same as placebo in one small study. Subjective measure showed that drug caused more severe dry mouth than placebo in another small study.
	Zimelidine	2	Worse than placebo in two small studies, although in one this was statistically non-significant
	Fluvoxamine	1	Objective measures showed that drug was the same as placebo in one small study.
Tetracyclic antidepressants (*k* = 6)	Mianserin	4	Depending on the study, objective measures showed that the drug caused more severe dry mouth than placebo, nomifensine, zimelidine, lithium and isocarboxazide with similar effects to other TCAs. Less severe dry mouth than amitriptyline objectively in one study and less than nortriptyline subjectively in another study. All but one of the studies were small.
	Maprotiline	2	Objective measures showed that drug caused more severe dry mouth than placebo in two small studies but was the same as chlorimipramine in one.
	Oxaprotiline	1	Objective measure showed that drug caused more severe dry mouth than placebo but less than amitriptyline (*n* = 308).
Monoamine oxidase inhibitors (*k* = 2)	Isocarboxazide	2	Objective measures showed that drug was the same as placebo in two small studies.
Norepinephrine–dopamine reuptake inhibitors (*k* = 2)	Nomifensine	2	Objective measures showed that drug caused more severe dry mouth placebo in two studies, although this was statistically non-significant in one. Depending on study, less than imipramine, nortriptyline or mianserin. Both studies were small.
Serotonin antagonist and reuptake inhibitors (*k* = 2)	Trazodone	2	Objective measure showed that drug caused more severe dry mouth placebo in one small study, although this was statistically non-significant. Less severe dry mouth than amitriptyline on subjective measures in another small study.
Norepinephrine reuptake inhibitors (*k* = 1)	Reboxetine	1	Objective and subjective measures showed that drug was the same as placebo in one small study.
Mood stabilisers (*k* = 2)	Lithium citrate	2	Objective measures showed that drug was the same as placebo in two small studies.

K, number of studies.

that are less used today. This makes it difficult for practitioners to seek guidance from research to manage patients on newer psychotropic drugs. The age of the studies could therefore indicate a lack of awareness in studying the oral side-effects of psychotropic drugs, and that the impact of dry mouth on the oral health of patients with psychiatric illnesses may have been neglected in recent years.

In addition, meta-analyses of our included studies were not possible owing to the heterogeneity of agents, subjects, study designs and outcome measures. In addition, many papers only presented graphical data without providing raw numbers. Although we used online digitisation software to estimate numerical values, our results should be viewed with caution. Ten of the 18 included studies did not report on blinding methods.

There were comparatively few studies for many of the agents, and in some cases (e.g. desipramine and citalopram) the evidence was contradictory. There was even less information on mood stabilisers and none on antipsychotics, although these were included in our search strategy. Importantly, there was no information on the most commonly used antidepressants, including escitalopram, paroxetine, fluoxetine, sertraline, duloxetine, venlafaxine and desvenlafaxine. Furthermore, most studies were of single doses in limited numbers of healthy subjects instead of individuals with psychiatric illness, which limits the generalisability of findings to clinical practice. For instance, people with psychiatric illness may be taking several other medications or have physical comorbidities that can exacerbate dry mouth. All but two of the studies were also very small, which may mean that they were underpowered to detect significant findings. These factors may mean that our findings underestimate the burden in psychiatric populations.

Last, few studies measured both objective and subjective dry mouth, which have different clinical implications. Objective dry mouth directly increases the risk of oral diseases, whereas both subjective and objective dry mouth may potentially reduce compliance owing to patients' inability to tolerate the adverse effects. Both objective and subjective measures are therefore important in providing guidance for practitioners in the management of patients' treatment adherence and risk of oral diseases.

Implications

Box 1 summarises the key implications. First, more research on newer psychotropic drugs is needed, particularly antipsychotics

https://doi.org/10.1192/bjo.2023.15 Published online by Cambridge University Press

Table 4 Risk-of-bias judgment for each of six domains of bias for each included study

	Study	Random sequence generation (selection bias) (high, low or unclear)	Allocation concealment (selection bias) (high, low or unclear)	Blinding of participants, personnel (performance bias) (high, low or unclear)	Blinding of outcome assessment (detection bias) (high, low or unclear)	Incomplete outcome data (attrition bias) (high, low or unclear)	Selective outcome reporting (reporting bias) (high, low or unclear)	Other sources of bias (high, low or unclear)
1	Arnold, 1981	Unclear	Low	Low	Low	High	Unclear	Unclear
2	Blackwell, 1972	Unclear	Low	Low	Low	Unclear	Unclear	Unclear
3	Botros, 1989	Unclear	Unclear	Low	High	Low	Unclear	Unclear
4	Bourne, 1993	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear
5	Clemmesen, 1984	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
6	Flett, 1992	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Unclear
7	Ghose, 1987	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
8	Guimarães, 1987	Unclear	Unclear	Low	Unclear	Low	Unclear	Unclear
9	Hoc, 1982	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear
10	Jang, 1991	Unclear	Unclear	Low	High	Low	Unclear	Unclear
11	Lader, 1986	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
12	Longmore, 1988	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
13	Penttila, 2001	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
14	Rafaelsen, 1981	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
15	Roffman, 1983	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear
16	Szabadi, 1980	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
17	Peterson, 1978	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
18	Ghose, 1976	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear

and commonly used antidepressants such as fluoxetine, sertraline, duloxetine, venlafaxine and desvenlafaxine. Second, the presentation of results should be standardised, and they should not be restricted to graphs but rather include numerical data that could be pooled for meta-analysis. Third, in order to increase the generalisability of findings to clinical practice, future research should involve participants with psychiatric illnesses. Last, future research should include both objective and subjective measures of dry mouth.

Box 1 Study implications

- Dry mouth is a common side-effect of many psychotropic medications.
- There is less information on differences in the severity of symptoms between agents, both subjectively or objectively measured using salivary flow.
- The present study was a systematic review of the literature on the severity of both subjective and objective dry mouth due to psychotropic drugs in adults.
- Eighteen RCTs with 605 participants were included, and severity was compared among eight drug classes and/or against placebo.
- All the studies were published 20 to 40 years ago and most investigated older drugs. As expected, TCAs caused more severe dry mouth, both objectively and subjectively, than placebo or newer agents.
- No information was available for antipsychotic medications or many of the commonly used antidepressants, and minimal information was available on mood stabilisers. This limits the generalisability of the study findings.
- The lack of research on the severity of psychotropic-induced dry mouth is surprising given its common occurrence; well-designed RCTs of newer psychotropic drugs are therefore indicated.
- The extensive use of SSRIs has shifted the focus away from xerostomia, although this is an important side-effect given the continuing role of TCAs in the treatment of both chronic pain and treatment-resistant depression.

Conclusion

This systematic review suggests that newer psychotropic drugs are associated with less severe dry mouth. However, this is based on very limited evidence. Given that TCAs are still an important medication for chronic pain and treatment-refractory depression,[51] both medical and dental practitioners should assess and manage the oral implications of dry mouth. This includes addressing other contributory factors (e.g. avoidance of caffeinated beverages, smoking cessation), advice on taking frequent sips of water throughout the day, and the use of oral lubricants, saliva substitutes or saliva stimulants, as well as management of any potential oral mucosal and dental complications. Finally, the lack of research on the severity of psychotropic-induced dry mouth is surprising given its common occurrence; well-designed RCTs of newer psychotropic drugs are therefore indicated.

Cherilyn Xue Wei Teoh, School of Dentistry, University of Queensland, Herston, Queensland, Australia; **Millie Thng**, School of Dentistry, University of Queensland, Herston, Queensland, Australia; **Serene Lau**, School of Dentistry, University of Queensland, Herston, Queensland, Australia; **Meng-Wong Taing**, School of Pharmacy, University of Queensland, Woolloongabba, Queensland, Australia; **Sarah Y. Chaw**, School of Dentistry, University of Queensland, Herston, Queensland, Australia; **Dan Siskind**, Metro South Addiction and Mental Health Service, Brisbane, Queensland, Australia; and School of Medicine, University of Queensland, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia; **Steve Kisely**, Metro South Addiction and Mental Health Service, Brisbane, Queensland, Australia; School of Medicine, University of Queensland, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia; and Departments of Psychiatry, Community Health and Epidemiology, Dalhousie University, Canada

Correspondence: Steve Kisely. Email: s.kisely@uq.edu.au

First received 29 Apr 2022, final revision 19 Jan 2023, accepted 20 Jan 2023

Supplementary material

Supplementary material is available online at http://doi.org/10.1192/bjo.2023.15.

https://doi.org/10.1192/bjo.2023.15 Published online by Cambridge University Press

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

Acknowledgements

None.

Author contributions

S.K. and M.-W.T. had the original idea for the paper. Study selection was conducted by C.X.W.T., M.T. and S.L. S.K. was available to resolve any differences between raters. Data extraction was conducted by C.X.W.T., M.T., S.L. and S.K. Another rater or D.S. was available to resolve any differences. M.-W.T., S.Y.C. and D.S. provided content expertise in relation to pharmacology, oral health and the treatment of mental illness, respectively. C.X.W.T., M.T. and S.L. jointly wrote the first draft. This was then revised critically for important intellectual content by the other authors. S.K. responded to the reviewers' comments.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of interest

None.

References

1 Plemons JM, Al-Hashimi I, Marek CL. Managing xerostomia and salivary gland hypofunction. *J Am Dent Assoc* 2014; **145**(8): 867–73.

2 Bardow A, Nyvad B, Nauntofte B. Relationships between medication intake, complaints of dry mouth, salivary flow rate and composition, and the rate of tooth demineralization in situ. *Arch Oral Biol* 2001; **46**(5): 413–23.

3 Tan ECK, Lexomboon D, Sandborgh-Englund G, Hassum Y, Johnell K. Medications that cause dry mouth as an adverse effect in older people: a systematic review and metaanalysis. *J Am Geriatr Soc* 2018; **66**(1): 76–84.

4 Cockburn N, Pradhan A, Taing MW, Kisely S, Ford PJ. Oral health impacts of medications used to treat mental illness. *J Affect Disord* 2017; **223**: 184–93.

5 Scully C. Drug effects on salivary glands: dry mouth. *Oral Dis* 2003; **9**(4): 165–76.

6 Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. *Eur J Clin Pharmacol* 2013; **69**(7): 1485–96.

7 Wolff A, Joshi RK, Ekström J, Aframian D, Pedersen AML, Proctor G, et al. A guide to medications inducing salivary gland dysfunction, xerostomia, and subjective sialorrhea: a systematic review sponsored by the world workshop on oral medicine VI. *Drugs R D* 2017; **17**(1): 1–28.

8 de Almeida PDV, Grégio AMT, Brancher JA, Ignácio SA, Machado MAN, de Lima AAS, et al. Effects of antidepressants and benzodiazepines on stimulated salivary flow rate and biochemistry composition of the saliva. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; **106**(1): 58–65.

9 Cappetta K, Beyer C, Johnson JA, Bloch MH. Meta-analysis: risk of dry mouth with second generation antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **84**(Part A): 282–93.

10 Friedlander A, Friedlander IK, Marder SR. Bipolar I disorder: psychopathology, medical management and dental implications. *J Am Dent Assoc* 2002; **133**(9): 1209–17.

11 Kisely S, Sawyer E, Siskind D, Lalloo R. The oral health of people with anxiety and depressive disorders a systematic review and meta-analysis. *J Affect Disord* 2016; **200**: 119–32.

12 Kisely S. No mental health without oral health. *Can J Psychiatry* 2016; **61**(5): 277–82.

13 Australian Institute of Health and Welfare. *Summary of Mental Health Services in Australia* (updated 20 Jul 2021). Australian Institute of Health and Welfare, 2021 (https://www.aihw.gov.au/reports/mental-health-services/mental-health-services-in-australia/report-contents/summary-of-mental-health-services-in-australia [cited 3 Sep 2021]).

14 Frank RG, Conti RM, Goldman HH. Mental health policy and psychotropic drugs. *Milbank Q* 2005; **83**(2): 271–98.

15 Steinhausen H-C. Recent international trends in psychotropic medication prescriptions for children and adolescents. *Eur Child Adolesc Psychiatry* 2015; **24**(6): 635–40.

16 Okamoto A, Miyachi H, Tanaka K, Chikazu D, Miyaoka H. Relationship between xerostomia and psychotropic drugs in patients with schizophrenia: evaluation using an oral moisture meter. *J Clin Pharm Ther* 2016; **41**(6): 684–8.

17 Kyu HH, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the global burden of disease study 2017. *Lancet* 2018; **392**(10159): 1859–922.

18 World Health Organization. *Mental Disorders*. WHO, 2019 (https://www.who.int/news-room/fact-sheets/detail/mental-disorders [cited 3 Sep 2021]).

19 Möller H-J, Bandelow B, Volz H-P, Barnikol UB, Seifritz E, Kasper S. The relevance of 'mixed anxiety and depression' as a diagnostic category in clinical practice. *Eur Arch Psychiatry Clin Neurosci* 2016; **266**(8): 725–36.

20 Madre M, Canales-Rodríguez EJ, Ortiz-Gil J, Murru A, Torrent C, Bramon E, et al. Neuropsychological and neuroimaging underpinnings of schizoaffective disorder: a systematic review. *Acta Psychiatr Scand* 2016; **134**(1): 16–30.

21 Royal Pharmaceutical Society. *Martindale: The Complete Drug Reference*. Royal Pharmaceutical Society (https://www-medicinescomplete-com.ezproxy.library.uq.edu.au/#/browse/martindale [cited 3 Sep 2021]).

22 Aravindhan R, Vidyalakshmi S, Kumar MS, Satheesh C, Balasubramanium AM, Prasad VS. Burning mouth syndrome: a review on its diagnostic and therapeutic approach. *J Pharm Bioallied Sci* 2014; **6**(1): S21–5.

23 National Health and Medical Research Council. *Assessing Risk of Bias*. National Health and Medical Research Council, 2019 (https://nhmrc.gov.au/guidelines-forguidelines/develop/assessing-risk-bias [cited 3 Sep 2020]).

24 Arnold SE, Kahn RJ, Faletta LL. Tricyclic antidepressants and peripheral anticholinergic activity. *Psychopharmacology* 1981; **74**(4): 325–8.

25 Blackwell B, Lipkin JO, Meyer JH, Kuzma R, Boulter WV. Dose responses and relationships between anticholinergic activity and mood with tricyclic antidepressants. *Psychopharmacologia* 1972; **25**(3): 205–17.

26 Botros WA, Ankier SI, Priest RG, McManus IC, Steinert J, Samir ZY. Clinical assessment and performance tasks in depression: a comparison of amitriptyline and trazodone. *Br J Psychiatry* 1989; **155**: 479–82.

27 Bourne M, Szabadi E, Bradshaw CM. A comparison of the effects of single doses of amoxapine and amitriptyline on autonomic functions in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44**(1): 57–62.

28 Clemmesen L, Mikkelsen PL, Lund H, Bolwig TG, Rafaelsen OJ.. Assessment of the anticholinergic effects of antidepressants in a single-dose cross-over study of salivation and plasma levels. *Psychopharmacology* 1984; **82**(4): 348–54.

29 Flett SR, Szabadi E, Bradshaw CM. A comparison of the effects of fluvoxamine and amitriptyline on autonomic functions in healthy volunteers. *Eur J Clin Pharmacol* 1992; **42**(5): 529–33.

30 Ghose K, Sedman E. A double-blind comparison of the pharmacodynamic effects of single doses of lofepramine, amitryptyline and placebo in elderly subjects. *Eur J Clin Pharmacol* 1987; **33**(5): 505–9.

31 Guimarães FS, Zuardi AW, Graeff FG. Effect of chlorimipramine and maprotiline on experimental anxiety in humans. *J Psychopharmacol* 1987; **1**(3): 184–92.

32 Hoc J. The clinical efficacy and side-effects of mianserin and nortriptyline in depressed out-patients: a double-blind randomized trial. *Curr Med Res Opin* 1982; **8**(4): 282–9.

33 Jang IJ, Shin JG, Shin SG, Kim JJ, Woo JI, Lee YS, et al. Assessment of the relationship between plasma nortriptyline concentration and inhibition of salivation – single-dose study. *Asia Pac J Pharmacol* 1991; **6**(3): 249–54.

34 Lader M, Melhuish A, Frcka G. The effects of citalopram in single and repeated doses and with alcohol on physiological and psychological measures in healthy subjects. *Eur J Clin Pharmacol* 1986; **31**(2): 183–90.

35 Longmore J, Banjar W, Bradshaw CM, Szabadi E. Effects of a controlled-release formulation of trazodone on psychomotor and autonomic functions in healthy volunteers: comparison with trazodone (conventional formulation), amitriptyline and placebo. *Eur J Clin Pharmacol* 1988; **34**(1): 97–9.

36 Penttilä J, Syvälahti E, Hinkka S, Kuusela T, Scheinin H. The effects of amitriptyline, citalopram and reboxetine on autonomic nervous system – a randomised placebo-controlled study on healthy volunteers. *Psychopharmacology* 2001; **154**(4): 343–9.

37 Peterson GR, Blackwell B, Hostetler RM. Anticholinergic activity of the tricyclic antidepressants despiramine and doxepin in nondepressed volunteers. *Commun Psychopharmacol* 1978; **2**(2): 145–50.

38 Rafaelsen OJ, Clemmesen L, Lund H. Comparison of peripheral anticholinergic effects of antidepressants: dry mouth. *Acta Psychiatr Scand* 1981; **63**(Suppl. 290): 364–9.

39 Roffman M, Gould E, Brewer S. Comparative anticholinergic activity of oxaprotiline and amitriptyline. *Drug Dev Res* 1983; **3**(6): 561–6.

40 Szabadi E, Gaszner P, Bradshaw CM. The peripheral anticholinergic activity of tricyclic antidepressants: comparison of amitriptyline and desipramine in human volunteers. *Br J Psychiatry* 1980; **137**: 433–9.

41 Ghose K, Coppen A, Turner P. Autonomic actions and interactions of mianserin hydrochloride (Org. GB 94) and amitriptyline in patients with depressive illness. *Psychopharmacology* 1976; **49**: 201–4.

https://doi.org/10.1192/bjo.2023.15 Published online by Cambridge University Press

42 Navazesh M, Christensen CM. A comparison of whole mouth resting and stimulated salivary measurement procedures. *J Dent Res* 1982; **61**(10): 1158–62.

43 Campisi G, Di Fede O, Roccia P, Di Nicola F, Falaschini S, Muzio LL. Saliva: its value as a biological matrix and current methods of sampling. *Eur J Inflamm* 2006; **4**(1): 11–9.

44 Navazesh M, Kumar SK. Measuring salivary flow: challenges and opportunities. *J Am Dent Assoc* 2008; **139**: 35S–40S.

45 Jongerius PH, van Limbeek J, Rotteveel JJ. Assessment of salivary flow rate: biologic variation and measure error. *Laryngoscope* 2004; **114**(10): 1801–4.

46 Jones JM, Watkins CA, Hand JS, Warren JJ, Cowen HJ. Comparison of three salivary flow rate assessment methods in an elderly population. *Community Dent Oral Epidemiol* 2000; **28**(3): 177–84.

47 Ahlner BH, Lind MG. A swab technique for sialometry. Normal range. *Acta Otolaryngol* 1983; **95**(1–2): 173–82.

48 Rohatgi A. WebPlotDigitizer, version 4.6. Ankit Rohatgi, 2022 (https://automeris.io/WebPlotDigitizer [cited 6 Sep 2022]).

49 Daly C. Oral and dental effects of antidepressants. *Aust Prescr* 2016; **39**(3): 84.

50 Moffat AK, Apajee J, Pratt NL, Blacker N, Le Blanc VT, Roughead EE. Use of medicines associated with dry mouth and dental visits in an Australian cohort. *Aust Dent J* 2020; **65**(3): 189–95.

51 Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry* 2007; **68**(8): 17.

https://doi.org/10.1192/bjo.2023.15 Published online by Cambridge University Press