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CLINICAL PHARMACOLOGY

The anticholinergic impregnation scale: Towards the elaboration of a scale adapted to prescriptions in French psychiatric settings

L'échelle d'imprégnation anticholinergique : vers l'élaboration d'une échelle adaptée aux prescriptions en milieu psychiatrique français

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Summary
Purpose. — Some drugs have anticholinergic activity and can cause peripheral or central side effects. Several scales exist to evaluate the potential anticholinergic effect of prescribed drugs but: (i) they are validated in the elderly and mainly assess the cognitive side effect of treatments; (ii) they do not concern some of the drugs frequently used in clinical psychiatry in France. The aim of our study is to develop a new scale, the anticholinergic impregnation scale (AIS), with drugs used in France and based on an assessment of the drugs used against peripheral anticholinergic adverse effects.

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Methods. — We assigned a score, ranging from 1 to 3, to a list of 128 drugs with a consensus approach obtained via literature data and expert opinions. We collected data from 7278 prescriptions in 34 French psychiatric facilities: age, sex, atropinic drugs, laxatives and treatments of xerophthalmia and xerostomia, in order to evaluate the association between AIS score and the prescription of drugs aiming to reduce peripheral anticholinergic side effects.
Results. — The most frequently prescribed drugs were cyamemazine ($n = 1429$; 20%) and tropatepine ($n = 1403$; 19%), two drugs marketed almost exclusively in France and with a score of 3. The frequency of patients with a high AIS score, greater than 5, was significantly higher in patients who received laxatives and treatments of xerostomia. AIS score represents the first validated solution to evaluate anticholinergic load in psychiatry settings in France.
Conclusion. — The anticholinergic problem remains underevaluated in mental health settings. In order to rule out the confounding factor of mental disease, assessment of peripheral side effects can be considered more objective than the evaluation of cognitive function in psychiatric patients. Building scales appropriate for each state also appear essential to obtain an useful and effective tool in clinical practice.

MOTS CLÉS
Anticholinergiques ;
Échelle de médicaments anticholinergiques ;
Psychiatrie

Résumé Certains médicaments ont une activité anticholinergique et peuvent provoquer des effets secondaires périphériques ou centraux. Plusieurs échelles existent pour évaluer l'effet anticholinergique potentiel des médicaments prescrits, mais : (i) elles sont validées chez les personnes âgées et principalement par le biais des effets cognitifs des traitements ; (ii) elles n'incluent pas certains médicaments fréquemment utilisés en France et notamment en psychiatrie. Le but de notre étude était de construire une nouvelle échelle, l'« échelle d'imprégnation anticholinergique » (EIA), intégrant les médicaments utilisés en France et sur la base d'une évaluation des médicaments prescrits pour lutter contre les effets indésirables anticholinergiques périphériques. Notre travail a permis la construction d'une liste de 128 médicaments : (i) avec une approche de consensus entre les données de la littérature et des avis d'experts et (ii) en s'appuyant pour sa validation sur 7278 prescriptions recueillies dans 34 établissements psychiatriques français.

Abbreviations

AAS	anticholinergic activity scale
ADS	anticholinergic drug scale
ACB	anticholinergic cognitive burden scale
AIS	anticholinergic impregnation scale
ARS	anticholinergic risk scale
ATC	anatomical therapeutic chemical class
CATIE	clinical antipsychotic trials of intervention effectiveness study
CI	confidence intervals
CrAS	clinician-related anticholinergic score
OR	odds ratio

Introduction

Drugs with anticholinergic activity are difficult to prescribe due to their multiple peripheral and central side effects, such as mydriasis, dry skin and mucous membrane, hyperthermia, urinary retention, constipation, tachycardia, confusion, attention deficit and memory impairment [1].

The main classes of anticholinergic drugs are tricyclic antidepressants, anticholinergic antihistaminics, antiparkinsonian drugs, neuroleptics, urinary antispasmodics, asthma medications and analgesic drugs. Elderly people are more vulnerable to anticholinergic effects because of polypharmacy, but also because aging results in a greater permeability of blood-brain barrier and an alteration of hepatorenal metabolism [2,3]. Thus, an association of drugs with anticholinergic properties in the elderly has to be prescribed with caution [4]. Anticholinergic load is also relevant to patients with mental illnesses because a great number of their treatments include anticholinergic properties [1,5,6]. These properties may cause peripheral or central side effects that are hard to distinguish from mental illness-related symptoms. However, the adverse effects related to drugs with anticholinergic activity are underevaluated in mental health settings. In order to exclude

the confounding factor of mental disease, assessment of peripheral side effects could be more useful in detecting anticholinergic load than neurocognitive assessment in patients with mental illnesses.

Several scales have been developed in the past years aiming to evaluate anticholinergic burden. Among them, seven scales can be considered relevant based on citation analysis [relevant articles have been selected according to inclusion/exclusion criteria defined by Salahudeen et al. [7]: the anticholinergic drug scale (ADS) [8,9], the anticholinergic risk scale (ARS) [10], the anticholinergic cognitive burden scale (ACB) [11], the anticholinergic burden classification (ABC) [12], the clinician-rated anticholinergic score (CrAS) [13], the anticholinergic activity scale (AAS) [14] and the anticholinergic loading scale (ACL)] [15]. The analysis of these questionnaires shows that:

- all scales are validated and used in the elderly;
- based on citation analysis, ACB, ARS, ADS and CrAS were the most frequently validated expert-based anticholinergic scales on adverse outcomes, but they have been validated in US drugs settings [7].

Most scales have also established their clinical validity based on the cognitive effects of specific drugs (ACB, AAS, ACL, ABC and CrAS). However, when the burden associated with anticholinergic drugs improves, it is not associated with alleviation of cognitive impairment in randomized clinical trials (mini review including in particular evaluations with: ARS, ACB and ADS) [16]. Moreover, in a cross-sectional analysis from 21 Norwegian nursing homes, high ADS scores were associated with peripheral but not cognitive markers of cholinergic blockade [17].

Taken together, these elements indicate that the evaluation of anticholinergic side effects in French mental health settings requires the development of a list of the most relevant prescription drugs in France (complemented by the assessment of the frequency of prescription of major drugs). In order to do so, we have created a new scale, the anticholinergic impregnation scale (AIS). In the present study, we conducted a multicenter evaluation of the association between AIS score and the prescription of drugs against peripheral anticholinergic side effects.

Methods

Population

We conducted a study in 34 French psychiatric facilities. Data were collected for each inpatient any given day in each facility. For each patient, the following data were collected: sex, age, illness chronicity and as needed prescriptions. This study was conducted using data collected on 7278 prescriptions.

Our study has a pragmatic design, so age and psychiatric diagnosis were not exclusion criteria. We focused on peripheral effects because central side effects are more difficult to interpret in patients with mental health conditions.

Scale elaboration

A list of 128 somatic and psychiatric drugs was created. Like previous studies with elderly subjects, our scale was built based on a mixed approach, including in vitro data of serum anticholinergic activity and clinician-rated scores. Both data present the respective limits of a theoretical pharmacological approach and a subjective human approach [15].

Similar to a model described in previous studies [15], we reported the previously published anticholinergic score for each drug, and transformed the observed score into our own scale score according to the following criteria:

- 1 — limited (including anticholinergic potential in vitro) or moderate effect;
- 2 — strong effect (including drugs with anticholinergic effect in high doses);
- 3 — very strong (including drugs with proven high anticholinergic potential).

For unrated drugs, classification was carried out on the same scale (1—3) based on independent ratings by 3 clinical pharmacists (2 PharmD and 1 PharmD, PhD) and 2 psychiatrists (2 MD). In case of discrepancy between published or clinician-rated scores, the median ranking was applied in order to rank the drugs.

Clinical value assessment of the scale

Aims of the study

As explained above, it is difficult to partial out the anticholinergic effects and the effects of the mental illness on cognition, we thus selected the prescription of drugs against peripheral anticholinergic side effects as an indirect indicator of anticholinergic burden. From this standpoint, we aimed at developing and evaluating whether our scale, specifically designed to evaluate drugs in French settings, is able to discriminate patients with ''high'' and ''low'' AIS scores.

Anticholinergic drugs and medications against anticholinergic peripheral side effects

For each prescription, in each facility, an (or some) investigator(s) (pharmacists or psychiatrists) collected:

- anticholinergic medications pertaining to the pre-established list of 128 drugs;
- medications, which were prescribed against anticholinergic peripheral side effects (xerostomia, xerophtalmia and constipation).

Three criteria were sought for each item, for laxatives: ''no'' (absence); ''one, with dose < maximum dose'' or ''several laxatives, or at least one with dose > maximum recommended dose'' and for treatments against xerostomia or xerophtalmia: ''no'' (absence); ''as needed'' or ''chronic''.

Drugs' prescribing frequency

The frequency of treatment prescriptions (prescribed systematically or ''as needed'') was assessed:

- to determine the relevance and the peculiarities of drugs prescribed exclusively or almost exclusively in France;
- to assess the amount of anticholinergic risk that helps the identification the anticholinergic burden of these drugs.

Statistics

All statistical analyses were performed using STATA® (Intercooled Stata 8, Stata Corp LLC, Texas, USA). A stepwise logistic regression was conducted with forward selection to assess association ($P < 0.05$) between AIS score > 5 (median value) and the variables age, sex, frequency of drugs against constipation, xerostomia and xerophtalmia. Odds ratios (OR) are presented with 95% confidence intervals (CI).

Results

The median AIS score was used as a threshold. AIS score was considered high if it was higher than 5. According to our classification, this cut-off corresponds to the combination of at least one drug with high anticholinergic activity and one drug with very high anticholinergic activity.

Scale elaboration

We created a list of 128 drugs with anticholinergic properties (AIS = 1: 70 drugs, AIS = 2: 23 drugs, AIS = 3: 35 drugs) (Table 1). Each drug has a score, which represents its anticholinergic potential. The drugs included: 19 antidepressants, 21 antipsychotics, mood stabilizers and antiepileptics, 9 anxiolytics or hypnotics, 14 H1-antihistamines, 10 antiparkinsonian drugs, 10 drugs for gastrointestinal disorders, 12 drugs related to cardiovascular illnesses, 6 analgesics, 6 antibiotics, 5 urinary antispasmodics, 5 corticoids, 3 muscle relaxants, 2 parasympatholytics or sympathomimetics, 2 immunosuppressants, 2 antiasthmatic drugs and 2 others drugs (Table 1 with anatomical therapeutic chemical [ATC] codes).

Clinical value assessment of the scale

Drugs' prescribing frequency

The treatments (Table 2) that are more frequently prescribed with a very strong anticholinergic effect (score 3) are:

- for drugs prescribed ''systematically'' (% of prescriptions): cyamemazine (20), tropatepine (19);
- for drugs prescribed ''as needed'' (% of prescriptions): cyamemazine (15), tropatepine (7), hydroxyzine (4).

The treatments that are more frequently prescribed with a strong anticholinergic effect (score 2) are:

- for drugs prescribed ''systematically'' (% of prescriptions): loxapine (18), olanzapine (10);
- for drugs prescribed ''as needed'' (% of prescriptions): levomepromazine (methotrimeprazine — 3).

The treatments that are more frequently prescribed with a limited or moderate anticholinergic effect (score 2) are:

- for drugs prescribed ''systematically'' (% of prescriptions): risperidone (17), diazepam (17), oxazepam (16), alimemazine (14), haloperidol (14) and valproic acid or sodium divalproex or valpromide (14);
- for drugs prescribed ''as needed'' (% of prescriptions): diazepam (10), alimemazine (9), oxazepam (7), alprazolam (4) and clorazepate (4).

Anticholinergic drugs and medications against anticholinergic peripheral side effects

Thirty-four mental health clinics participated with 7278 patients (48—517 per center), women (42%) and men (58%), aged between 1 and 102 years (mean = 50). The median AIS score was 6 (mean = 6.8 ± 4.01) for all prescriptions (chronic and as needed) and 5 (mean = 5.03 ± 3.12) for chronic prescriptions only. The median number of anticholinergic medications was 4 (0—14). Only 2.76% of patients had a AIS score equal to 0. The median score was chosen to separate patients in two groups: low scores (≤ 5) and high scores (> 5). Results of logistic regression are presented in Table 3. Reference modalities are: men, age ≤ 17 years, no prescription of laxatives, no prescription of drugs against xerostomia. The frequency of patients with an AIS score greater than 5 was significantly higher in men, patients who received laxatives and in patients who received drugs against xerostomia ($P < 0.0001$). Prescription of lubricant eye drops was not statistically associated with highest scores.

Discussion

In a recent review, 7 scales were shown to be relevant in order to evaluate anticholinergic burden [7]: ADS, ARS, ACB, ABC, CrAS, AAS and ACL. Theses scales are well suited to elderly populations and generally assess cognitive side effects. However, neurocognitive assessment is less reliable in patients with psychiatric illnesses and recent data suggest that the use of validated anticholinergic rating scales based on the peripheral effects might be particularly important [17]. Moreover, most scales have been validated in US drugs settings [7]. Thus, the assessment of the anticholinergic burden of French prescriptions is not satisfying based on the current available tools.

Published data on anticholinergic load in psychiatric settings is fairly limited. Most of the available data concern the anticholinergic effects of psychotropic drugs presented by class; they focus mainly on antipsychotics and [1,18—20], less often on antidepressants [21]. To our knowledge, the largest study to date that focused on the anticholinergic burden in psychiatry was made by Minzenberg et al. [5]. Their study involved 106 patients with schizophrenia who had had a neuropsychological assessment and clinician-rated scores of the effects of their prescribed treatments. Therefore, it is crucial to take into account two variables that might affect prescriptions: whether they were prescribed in psychiatric settings, and in which country the prescriptions were made. To our knowledge, there were no available scales aiming at assessing anticholinergic burden in psychiatric settings in France.

Thus, in order to elaborate a scale that was well suited to the French psychiatric context, we created an extensive list of 128 drugs with anticholinergic properties (with scores ranging from 1 to 3 points) (Table 1). The drugs included comprised 19 antidepressants, 17 antipsychotics and mood stabilizers, 15 antihistaminics, 10 antiparkinsonian drugs and 8 anxiolytics or hypnotics to ensure an optimal evaluation of psychiatric prescriptions.

Anticholinergic scores obtained in our study are higher than those reported in previous studies. Moreover, the

Table 1 Anticholinergic Impregnation Scale scoring for 128 drugs.

Pharmacologic groups	ATC Code	International non-proprietary name	AIS score	Data from [6]	Data from [7]
Antidepressants (19)	N06A	Amitriptyline[a,b,c,d]	3	H	H
		Amoxapine[c]	3	H?	H
		Bupropion[c,d]	1	L?	L
		Citalopram	1	L	L
		Clomipramine[b,c]	3	H	H
		Dosulepine	2	L	M
		Doxepine[c,d]	3	H	H
		Duloxetine	1	L?	—
		Fluoxetine[b,d]	1	L	L
		Fluvoxamine[b,c]	1	L	L
		Imipramine[a,b,c,d]	3	H	H
		Maprotiline	3	H?	H
		Mirtazapine[a]	1	L	L
		Nortriptyline[b,c,d]	3	H	H/M
		Paroxetine[d]	2	L	H/M/L
		Phenelzine[b]	1	L	L
		Sertraline[b,d]	1	0	L
		Trazodone[a,c,d]	1	L	L
		Trimipramine[b,c]	3	H	H
Antipsychotics, normothymics and antiepileptics (21)	N05A	Clozapine[b,c]	3	H	H/M
		Chlorpromazine[a,b,d]	3	H	H
		Cyamemazine	3	—	—
		Fluphenazine[a]	3	H	H/L
		Haloperidol[a,c]	1	L	M/L
		Levomepromazine (methotrimeprazine)	2	H	H
		Lithium	1	L	L
		Loxapine[b,c]	2	L	M
		Olanzapine[a]	2	L	H/M/L
		Perphenazine[a,c]	3	H?	H/M/L
		Pimozide[b,c]	2	L	M
		Pipotiazine	1	—	—
		Prochlorperazine[a,d]	2	L	M/L
		Propericiazine	1	—	—
		Quetiapine[c,d]	2	L	H/M/L
		Risperidone[b,c,d]	1	L	L
	N03	Sodium divalproex[b]/valpromide	1	L?	L
		Valproic acid[b]	1	L?	L
		Carbamazepine[b,c]	2	0	M/L
		Clonazepam[b]	1	L	L
		Oxcarbazepine[b,c]	2	L	M
Anxiolytics or hypnotics (9)	N05B	Alprazolam[b,c,d]	1	H?	H/L
		Chlordiazepoxide[b,d]	1	L	L
		Clorazepate[b,c]	1	H?	H/L
		Diazepam[b,c,d]	1	L	L
		Lorazepam[b]	1	L?	L
		Oxazepam[b]	1	L?	L
		Hydroxyzine[a,b,c,d]	3	H	H
	N05C	Midazolam[b]	1	L?	L
		Temazepam[b]	1	L	L

Table 1 (*Continued*)

Pharmacologic groups	ATC Code	International non-proprietary name	AIS score	Data from [6]	Data from [7]
H1-antihistamines (14)	R06A	Alimemazine[c]	1	L	M/L
		Brompheniramine[b]	3	H	H
		Cetirizine[a,d]	2	L	M/L
		Chlorphenamine[a,b,c,d]	3	—	H
		Cyproheptadine[a]	3	H	H/M
		Desloratadine	3	—	L
		Dexchlorpheniramine	3	H	H
		Diphenhydramine[a,b,c,d]	3	H	H
		Doxylamine	2	—	H
		Fexofenadine[d]	2	L	M
		Loratadine[a]	2	L	M/L
		Mequitazine	3	—	—
		Promethazine[a,b,c]	3	H	H
		Triprolidine[a]	2	—	—
Antiparkinsonian (10)	N04	Amantadine[a,c]	2	L	M/L
		Biperiden	3	—	—
		Bromocriptine[b]	1	L	L
		Carbidopa[a,d]	1	L?	L
		Entacapone[a]	1	L	L
		Levodopa[a]	1	0	—
		Pramipexol[a]	1	L?	L
		Selegiline[a]	1	L?	L
		Trihexyphenidyle[b,c,d]	3	H	H
		Tropatepine	3	H	H
Drugs for gastrointestinal disorders (10)	A02	Cimetidine[a,b]	2	L	M/L
		Famotidine[b]	1	L?	L
		Nizatidine[b]	1	—	—
		Ranitidine[b]	1	L	M/L
	A03	Alverine[c]	1	L?	M/L
		Atropine[a,c,d]	3	H	H
		Domperidone	1	L	L
		Metoclopramide[a]	1	H?	L
	A06	Dimenhydrinate[b,c]	3	H	H
	A07	Loperamide[a]	2	L	M/L
Drugs related to cardiovascular system (12)	B01	Warfarin[a,b,c]	1	0	L
	C01	Digoxin[b,c]	1	H?	H/L
		Disopyramide[b]	2	L	M/L
		Isosorbide[b,c]	1	L?	L
		Quinidine[c]	1	—	L
	C03	Chlortalidone[b,c]	1	L?	L
		Triamterene[b,c]	1	L?	L
	C07	Atenolol[c]	1	0	L
		Metoprolol[c,d]	1	0	L
	C08	Diltiazem[b]	1	L?	L
		Nifedipine[b,c]	1	0	L
	C09	Captopril[b,c]	1	L?	L
Analgesics (6)	N02	Codeine[b,c,d]	1	L	M/L
		Fentanyl[b,c]	1	L	L
		Morphine[b,c,d]	1	L	L
		Oxycodone[b,d]	1	L	L
		Pethidine[d]	2	—	—
		Tramadol[b]	1	L	M/L

Table 1 (*Continued*)

Pharmacologic groups	ATC Code	International non-proprietary name	AIS score	Data from [6]	Data from [7]
Antibiotics (6)	J01	Ampicilline[b]	1	L?	L
		Cefoxitin[b]	1	L?	L
		Clindamycine[b]	1	L?	L
		Gentamicine[b]	1	L?	L
		Piperacilline[b]	1	L?	L
		Vancomycine[b]	1	L?	L
Urinary antispasmodics (5)	G04	Flavoxate[b,c]	3	H	H
		Oxybutynine[a,b,c]	3	H	H/M
		Solifenacine	3	—	H
		Tolterodine[b,c]	3	H	H/M
		Trospium	3	—	H
Corticoids (5)	H02	Dexamethasone[b]	1	L?	L
		Hydrocortisone[b,c]	1	L?	M
		Methylprednisolone[b]	1	L?	L
		Prednisone/prednisolone[b,c]	1	—/L	L/L
		Triamcinolone[b]	1	L?	L
Muscle relaxants (3)	M03	Baclofen[a,d]	2	L	M
		Methocarbamol[a,d]	1	L	L
		Tizanidine[a]	3	H	H
Parasympatholytics or sympathomimetics (2)	A04	Scopolamine[b,c,d]	3	H	H
	R01	Pseudoephedrine[a]	2	L?	M
Immunosuppressants (2)	L04	Azathioprine[b]	1	L?	L
		Cyclosporin[b]	1	L?	L
Antiasthmatic drugs (2)	R03	Ipratropium	3	H	H
		Theophylline[b,c]	1	L	M/L
Others (2)	N02	Methadone[d]	2	L	M
	M04	Colchicine[c]	1	H?	H/L

Comparisons with the latest reviewed data in the literature: Duran et al. (2013) [6] (H for ''high potency anticholinergics'', H? for ''strong discrepancies in highly-scored drugs, not confirmed in Martindale®''), L for ''low potency anticholinergics'', L? for ''discrepancies in drugs that received low grades, not confirmed in Martindale®'' and 0 for drugs with ''improbable anticholinergic action'' and Salahudeen et al. (2015) [7] (H: high anticholinergic activity medicines, M: moderate anticholinergic activity medicines, L: low anticholinergic activity medicines and H/M, H/M/L, H/L and M/L — corresponding to the previous abbreviations — refer to drugs with ''inconsistent validation''); ''—'' means unavailable data in the two articles. ATC code: anatomical therapeutic chemical code. A02 — Drugs for acid related disorders, A03 — Drugs for functional gastrointestinal disorders, A04 — Antiemetics and antinauseants, A06 — Drugs for constipation, A07 — Antidiarrheals, intestinal anti-inflammatory/anti-infective agents, B01 — Antithrombotic agents, C01 — Cardiac therapy, C03 — Diuretics, C07 — Beta blocking agents, C08 — Calcium channel blockers, C09 — Agents acting on the renin-angiotensin system, G04 — Urologicals, H02 — Corticosteroids for systemic use, J01 — Antibacterials for systemic use, L04 — Immunosuppressants, M03 — Muscle relaxants, M04 — Antigout preparations, N02 — Analgesics, N03 — Antiepileptics, N04 — Antiparkinson drugs, N05 — Psycholeptics, N05B — Anxiolytics and N05C — Hypnotics and sedatives, N06 — psychoanaleptics, N06A — Antidepressants, N05 — Psycholeptics, N05A — Antipsychotics, R01 — Nasal preparations, R03 — Drugs for obstructive airway, R06A — Antihistamine for systemic use.

[a] ARS (Anticholinergic Risk Scale; Rudolph et al., [10]).
[b] ADS (Anticholinergic Drug Scale; Carnahan et al., [8,9]).
[c] ACB (Anticholinergic Cognitive Burden Scale; Boustani et al., [11]).
[d] CrAS (Clinician-rated Anticholinergic Score; Han et al., [13]).

Table 2 Twelve anticholinergic drugs most prescribed (systematically or as needed).

Drugs prescribed ''systematically''			Drugs prescribed ''as needed''		
Drugs	AIS score	*n* (%)	Drugs	AIS score	*n* (%)
Cyamemazine	3	1429 (20)	Loxapine[b,c]	2	1516 (21)
Tropatepine[e]	3	1403 (19)	Cyamemazine	3	1089 (15)
Loxapine[b,c]	2	1295 (18)	Diazepam[b,c,d,f]	1	737 (10)
Risperidone[a,c,d,g]	1	1272 (17)	Alimemazine[c,e]	1	651 (9)
Diazepam[b,c,d,f]	1	1206 (17)	Tropatepine[e]	3	508 (7)
Oxazepam[b,g]	1	1139 (16)	Oxazepam[b,g]	1	504 (7)
Alimemazine[c,e]	1	1038 (14)	Hydroxyzine[a,b,c,e]	3	324 (4)
Haloperidol[a,c,g]	1	1022 (14)	Alprazolam[b,c,d,e,g]	1	270 (4)
Valproic acid or sodium divalproex or valpromide[b]	1	986 (14)	Clorazepate[b,c,e]	1	266 (4)
Olanzapine[a,b,c,d,f]	2	761 (10)	Levomepromazine (methotrimeprazine)[b,c,e]	2	220 (3)

Letters underlined if the scale gives the same score that AIS.
[a] ARS (Anticholinergic Risk Scale; Rudolph et al. [10]).
[b] ADS (Anticholinergic Drug Scale; Carnahan et al. [8,9]).
[c] ACB (Anticholinergic Cognitive Burden Scale; Boustani et al. [11]).
[d] CrAS Clinician-rated Anticholinergic Score; Han et al. [13]).
[e] ABC (Anticholinergic Burden Classification; Ancelin et al. [12]).
[f] AAS (anticholinergic activity scale; Ehrt et al. [14]).
[g] ACL (anticholinergic loading scale; Sittironnarit et al. [15]).

amount of anticholinergic drugs per prescription is higher than those found in other studies [22—25]. However, the available data showed results of studies with elderly people in geriatric settings with very different prescription characteristics. For example, Fox et al. [22] conducted a large study, which included 13,004 participants (mean age: 75.2 ± 6.8), and showed a mean on the ACB score of 1.8 ± 1.1 (6.08 ± 4.01, for AIS in our study) and 52% of patient had an ACB score equal to 0 (only 2.76% had AIS score equal to 0 in our study). These data, similar to others available in the literature, highlight the need of specific studies in psychiatric settings with patients younger than 65 years.

Table 3 Estimated odds ratio (OR) of high scores anticholinergic impregnation scale (AIS) [> 5] for variables retained by logistic regression.

	AIS score > 5	AIS score ≤ 5	OR [CI (95%)]	*P*-value
Sex				
Men	1912 (45.40%)	2299 (54.60%)	0.71 [0.64—0.79]	< 0.0001[a]
Women	1123 (36.62%)	1944 (63,38%)		
Age				
≤ 17 years	26 (27.96%)	67 (72,04%)	1.68 [1.04—2.70]	< 0.0001[b]
18—64 years	2640 (46.71%)	3012 (53,29%)		
≥ 65 years	369 (24.07%)	1164 (75,93%)	0.53 [0.32—0.86]	< 0.0001[b]
Laxatives				
No use	1284 (33.98%)	2495 (66,02%)	2.03 [1.81—2.28]	< 0.0001[c]
Prescription of one laxative, with dose < maximum recommended dose	1015 (47.10%)	1140 (52.90%)		
Prescription of several laxatives, or at least 1 with dose > maximum recommended dose	736 (54.76%)	608 (45,24%)	2.74 [2.39—3.14]	< 0.0001[c]
Treatments against xerostomia				
No use	2517 (38.49%)	4023 (61,51%)	3.38 [2.84—4.01]	< 0.0001[c]
Use	518 (70.19%)	220 (29,81%)		

CI (95%): 95% confidence interval.
[a] Reference: men.
[b] Reference: ≤ 17 years.
[c] Reference: no use.

In our study, a high anticholinergic burden (AIS score > 5) was associated with a higher rate of prescription of two anticholinergic side effects correctors: laxatives and drugs against xerostomia. Hugues et al. [26] found in 182 senior care home residents in Australia that greater anticholinergic load was associated with numerous side effects, including hypertension, dry mouth, dry eyes, constipation and urinary hesitancy. Many psychotropic treatments may induce constipation (as antidepressants or certain antipsychotics and mood stabilizers). Among antidepressants, tricyclic antidepressants induce more frequently constipation and are associated with very high anticholinergic scores, while among the mood stabilizers, carbamazepine and oxcarbazepine, associated with elevated anticholinergic scores, exhibit higher risks of constipation compared to valproic acid and lamotrigine. Talley et al. [27] studied risk factors for chronic constipation based on three large samples of patients [patients diagnosed with chronic constipation ($n = 7251$), patients diagnosed with constipation of unspecified chronicity ($n = 6441$), and controls ($n = 7103$)]; antidepressants and anticonvulsants were associated with the highest risk among drugs, but not antipsychotics. Although constipation has globally received little attention in studies conducted in psychiatry, it has been frequently reported with atypical antipsychotics in their association with anticholinergic agents [28]. However, atypical antipsychotics are also well-known to induce constipation linked to their anticholinergics activities. Among them, clozapine, olanzapine, loxapine and quetiapine show a higher risk compared to haloperidol, risperidone and aripiprazole [28]. In phase 3 of the clinical antipsychotic trials of intervention effectiveness (CATIE) study, anticholinergic side effects (urinary hesitancy, dry mouth and constipation) occurred in a similar prevalence between typical and atypical antipsychotics, 15% versus 18%, respectively [29]. Moreover, plasma concentrations of olanzapine are higher in patients who have reported anticholinergic side effects in the past, especially constipation [30]. Although xerostomia may occur by various ways (modulations activities of muscarinic, alpha-adrenergic, serotoninergic or benzodiazepines receptors), anticholinergic side effects with blockage of the muscarinic M3 receptors remains a strong pharmacological explanation [31]. Kersten et al. [17] reported that patients with ADS scores ≥ 6 expressed a 0.7-fold lower saliva production compared to patients with an ADS score of 3.

Among the 12 anticholinergic drugs most prescribed in France (Table 3):

- for drugs prescribed systematically, cyamemazine and tropatepine are the two most commonly prescribed (20% and 19% of prescriptions, respectively) and they have a very high AIS score;
- for medication prescribed ''as needed'', cyamemazine and tropatepine are the second and fifth most frequently prescribed drugs, respectively (15% and 7% of prescriptions, respectively).

Furthermore, loxapine, which presents a strong AIS score, is the third treatment most prescribed systematically and the most frequently prescribed treatment ''as needed'' (18% and 21% of prescriptions, respectively). Cyamemazine marketed in France and Portugal is the most systematically prescribed treatment and presents a very strong anticholinergic load; it is incorporated into the present in any rating scale anticholinergic load. Tropatepine marketed only in France is the second most frequently systematically prescribed treatment and has a very strong anticholinergic load; it is only integrated in the ABC scale [12]. These data show the importance of a validated scale with these molecules in order to achieve a reliable evaluation of the anticholinergic burden in psychiatric services in France, due to the existence of very local and strong anticholinergics agents, frequently prescribed in France (and often considered obsolete by other drug agencies in the world).

The use of a system to alert the prescriber of anticholinergic load may lead to a decrease of anticholinergic prescriptions [25]. Therefore, this new list could help prescribers to reduce anticholinergic load in patients although it does not allow the prediction of the occurrence of side effects.

The score was used in French hospitals, through this study, to evaluate prescriptions practice, to educate prescribers regarding anticholinergic load. It was important also to educate nurses who, on the one hand, may have an impact on the overall anticholinergic load via as needed prescription, and, on the other hand, are often the first to hear about complaints concerning constipation, dry mouth or dry eyes.

There are two major limitations in our study. First, we did not take dosage ranges into consideration in the calculation exposure. Second, we assume that the treatments against side effects were prescribed due to anticholinergic burden.

Conclusion

Prescribers in psychiatric settings must keep in mind anticholinergic burden, since numerous psychotropic drugs present with anticholinergic properties and, high anticholinergic load is, in turn, associated with the increase of peripheral or central anticholinergic side effects.

This AIS score of anticholinergic drugs represents the first validated solution to assess anticholinergic load in French psychiatry because of ''typically French'' drugs, such as cyamemazine and tropatepine were integrated in it. These drugs exhibited a high anticholinergic score, and were used on this original validation integrating evaluation of the prescription of drugs against peripheral anticholinergic side effects.

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Disclosure of interest

The authors declare that they have no competing interest.

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