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Research Report

CHROME Criteria and Quality of Life: A Pilot Study from Maria Wolff-Albertia

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Abstract.
Background: Over- and potentially inappropriate prescribing of psychotropic medications is a major public health concern among people with dementia.
Objective: Describe the **CH**emical **R**estraints av**O**idance **ME**thodology (CHROME) criteria and evaluate its effects on psychotropic prescribing and quality of life (QoL).
Methods: Observational, prospective, two-wave study conducted in two nursing homes. A multicomponent program to eliminate chemical restraints and attain quality prescription of psychotropic medications was implemented. CHROME's diagnostic criteria comprise constellations of behavioral and psychological symptoms of dementia under six primary syndromic diagnoses. Since pharmacologic treatment is aimed at only one syndrome, polypharmacy is avoided. Psychotropic prescription, QoL, neuropsychiatric symptoms (NPS), and other clinical measurements were collected before and one year after the intervention. Results are presented for all residents ($n = 171$) and for completer subjects ($n = 115$).
Results: Mean age (SD) of the residents was 87.8 (5.7), 78.9% were women, and 68.5% suffered advanced dementia. Psychotropic prescriptions decreased from 1.9 (1.1) to 0.9 (1.0) ($p < 0.0005$). Substantive reduction in prescribing frequency was observed for antidepressants (76.9% pre-intervention, 33.8% post-intervention) and for atypical neuroleptics (38.8% pre-intervention, 15.1% post-intervention). There was improvement in patient's response to surroundings ($p < 0.0005$) and total NPS ($p < 0.01$), but small worsening occurred in social interaction ($p < 0.02$, completer subjects). Safety measurements remained stable.
Conclusion: CHROME criteria appear to optimize psychotropic prescriptions, avoid chemical restraints, and allow external verification of quality prescriptions. Extensive use seems feasible, related to substantial reduction of prescriptions, and of benefit for people with dementia as de-prescriptions are not associated to increased NPS or QoL loss.

Keywords: Chemical restraint, dementia, neuropsychiatric symptoms, nursing home, psychotropic medications, quality of life

INTRODUCTION

People with dementia are often prescribed psychotropic medications, despite limited efficacy and serious safety concerns, especially for neuroleptics

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and benzodiazepines [1–6]. High frequency of neuroleptic prescribing has been particularly reported in nursing homes [4, 7], together with potentially inappropriate use [7, 8].

Over-prescription of psychotropic drugs is a multifaceted phenomenon, not yet well understood. On many occasions, it may arise from a false belief that medications may solve behavioral or psychological problems more conveniently than with non-pharmacological means. Previous studies examined the association between neuropsychiatric symptoms (NPS) and psychotropic prescribing, but the strength of the association was limited [9], suggesting inappropriate or off-label use [10].

Several medical, societal, and economic factors may be influencing overprescribing of psychotropic medications in people with dementia living in nursing homes. Some of these factors are diagnostic errors [10, 11], treatment errors [12], and lack of constrained treatment periods or periodic treatment evaluation [13]. In addition, psychotropics may also be utilized for other indications (e.g., antidepressants and antiepileptics may be used for pain control).

Evidence of significant risks arising from short- and, particularly, long-term use of neuroleptics and other psychotropic medications led to an emphasis on deprescribing rather than pharmacological optimization [14, 15]. Several factors have been reported to influence deprescribing, including not only scientific evidence, but also social factors such as physician receptivity, residents' goals of care, limited training, time constraints, and lack of interdisciplinary collaboration, among others [16–18].

In contrast to pure deprescribing, medication optimization is aimed at ensuring the safest and most effective use of medications [19]. Optimization, which implicitly includes deprescribing, thereby adds to quality prescribing. In this regard, a range of approaches have been proposed, from medical approaches based on efficacy and safety balance [20–22] to global approaches that include education and counseling for physicians, nurses, and nurse aids [23]. Global approaches usually implement environmental adaptation from a person-centered perspective, sometimes combined with non-pharmacological therapies [24], keeping pharmacological treatment for the more resistant or severe cases.

The **CH**emical **R**estraints av**O**idance **ME**thodology (CHROME) criteria were designed as a comprehensive and explicit methodology to guide, evaluate, and certify quality prescribing of psychotropic medications for people with dementia. By including an *ad hoc* definition of chemical restraint, the CHROME approach also pursues the elimination of overprescribing and chemical restraints (Supplementary Material 1).

While interventions aiming at prescribing reduction, as well as CHROME implementation, were proven safe [2, 11], very few studies analyzed the effects of those interventions on NPS or quality of life (QoL) [25, 26]. This paucity in research is striking, as psychotropics are primarily prescribed with the goal of symptomatic improvement of both areas.

In this paper, we will describe the rationale and development of the CHROME criteria, along with the results of their implementation in a pilot study where frequency of prescription, NPS, and QoL were measured.

MATERIALS AND METHODS

CHROME development and description

As inappropriate prescribing and overprescribing appear because of so many contributing factors, CHROME, first devised in 2016 [27] and validated in 2019 [11] has multiple components, which can be structured in four functional groups: 1) *Quality prescribing,* 2) *Patient rights and legal compliance,* 3) *Pharmacy,* and 4) *External audit and certification of CHROME compliance*. Specifically, CHROME criteria substitute the traditional symptom-based prescription approach with explicit neuropsychiatric syndrome diagnostic criteria and their subsequent prescription recommendations (Table 1).

CHROME syndromic approach is consistent with the standards of diagnosis in Psychiatry, which relies on symptom constellations and expert consensus, rather than biomarkers [28, 29]. Since the focus was on pharmacological treatment, six relevant syndromes were defined based on specific treatment response observed in non-demented patients. To define these CHROME syndromes, we utilized previously published clinical pictures [30–32], although the diagnostic process was streamlined to allow feasibility in usual clinical practice. In line with the procedures of the Diagnostic and Statistical Manual of Mental Disorders [28], diagnosis was based on core symptoms, temporal pattern, exclusion criteria, and clinician judgment. As specific contributions, the spectrum of agitation/aggression was narrowed down and the maniform (that is, manic-like) syndrome was separately defined, according to distinct semiology and treatment response [33, 34]. A complete rationale

Table 1
Neuropsychiatric syndromes and indicated medications

	Core symptoms[1]	Duration	Indicated medications
Depression	Sadness, anhedonia, lack of hope	Most of the time for the last two weeks	- SSRI, SNRI, other antidepressants (mirtazapine, vortioxetine, bupropion)
Anxiety	Excessive/unjustified fear, feeling of loss of control, somatic complaints, repetitive thoughts or behaviors	Most of the time for the last two weeks	- SSRI, SNRI, other antidepressants (mirtazapine, trazodone) - Short/middle half-life BZD, gabapentin, pregabalin[2] - Atypical antipsychotics[3]
Psychotic syndrome	False beliefs or stories (ideas of theft, abandonment, prejudice, infidelity, etc.) or false perceptions (visual, auditory, etc.)	Most days for the last seven days	- Atypical antipsychotics
Impulsive syndrome	Lack of foresight or social tact	Most of the time for the last two weeks	- Serotoninergic medications (sertraline, citalopram, escitalopram, trazodone) - Antiepileptic drugs (valproate, gabapentin, pregabalin, carbamazepine, oxcarbamazepine, zonisamide), atypical antipsychotics[2]
Maniform syndrome	Elevated mood, overestimation of own capabilities, feeling abnormally energetic, hyperactive, decreased need for rest	Most of the time for the last week	- Antiepileptic drugs (valproate, carbamazepine, oxcarbamazepine, topiramate), atypical antipsychotics (e.g., quetiapine) - Lithium[2]
Sleep disturbance	Loss of the physiological sleep-wake cycle (hypersomnia, insomnia, cycle inversion, fragmented sleep, etc.)	Most days for the last two weeks	- Short half-life benzodiazepines (lorazepam, lormetazepam), benzodiazepine analogs (zolpidem, zopiclone), other medications (clomethiazole, trazodone, mirtazapine, gabapentin, pregabalin, melatonin), natural products (valeriana, passiflora) - Atypical antipsychotics (quetiapine, olanzapine)[2]

[1]To qualify for diagnosis, symptoms should produce significant distress, loss of functioning, or risk; in addition, symptoms should not be a mere consequence of cognitive deterioration, medical process, unmet basic needs, inadequate environment, or other neuropsychiatric symptom; [2]second choice; [3]last choice. BZD, benzodiazepines; SNRI, Serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

of each CHROME syndrome was published elsewhere [35].

CHROME methodology combines deprescribing and syndrome-specific prescribing (Fig. 1). In case of patients receiving several psychotropic medications, deprescribing should invariably come first. Once indicated treatment is started, response and safety must be systematically monitored. Treatment benefits should be noticeable within 1–3 days of starting or increasing dose in the case of benzodiazepines, while up to one month of treatment may be necessary to observe positive effects of antidepressants. Vital signs, arousal, cognition, functional status, affective and behavioral symptoms, as well as patient-specific medical conditions, should be closely monitored, particularly during the first weeks of treatment or dose increase. A reliable informant having daily contact with the patient is useful and, in most cases, necessary to evaluate treatment response. Reduction of frequency or severity of symptoms qualifies as a positive response. Treatment is considered successful if improvement in symptoms outweighs unwanted adverse effects, provided a reasonable dose has been reached; failure if the opposite is the case. Even in case of success, treatment reduction or withdrawal should be periodically considered (for more details on CHROME-based prescription and chemical restraint elimination see Supplementary Material 1).

Study design

This was an observational, prospective, two-wave study conducted in two nursing homes from Albertia under usual care and practice conditions. Albertia Servicios Sociosanitarios is a chain of 14 nursing homes spread throughout Spain. In Spring 2018, its CEO and Medical Director (LP) decided to implement the CHROME chainwide. The present study reports the findings of two homes (Albertia "Valle de la Oliva" and Albertia "Las Palmeras") located in the outskirts of the greater metropolitan area of Madrid. These two homes were audited

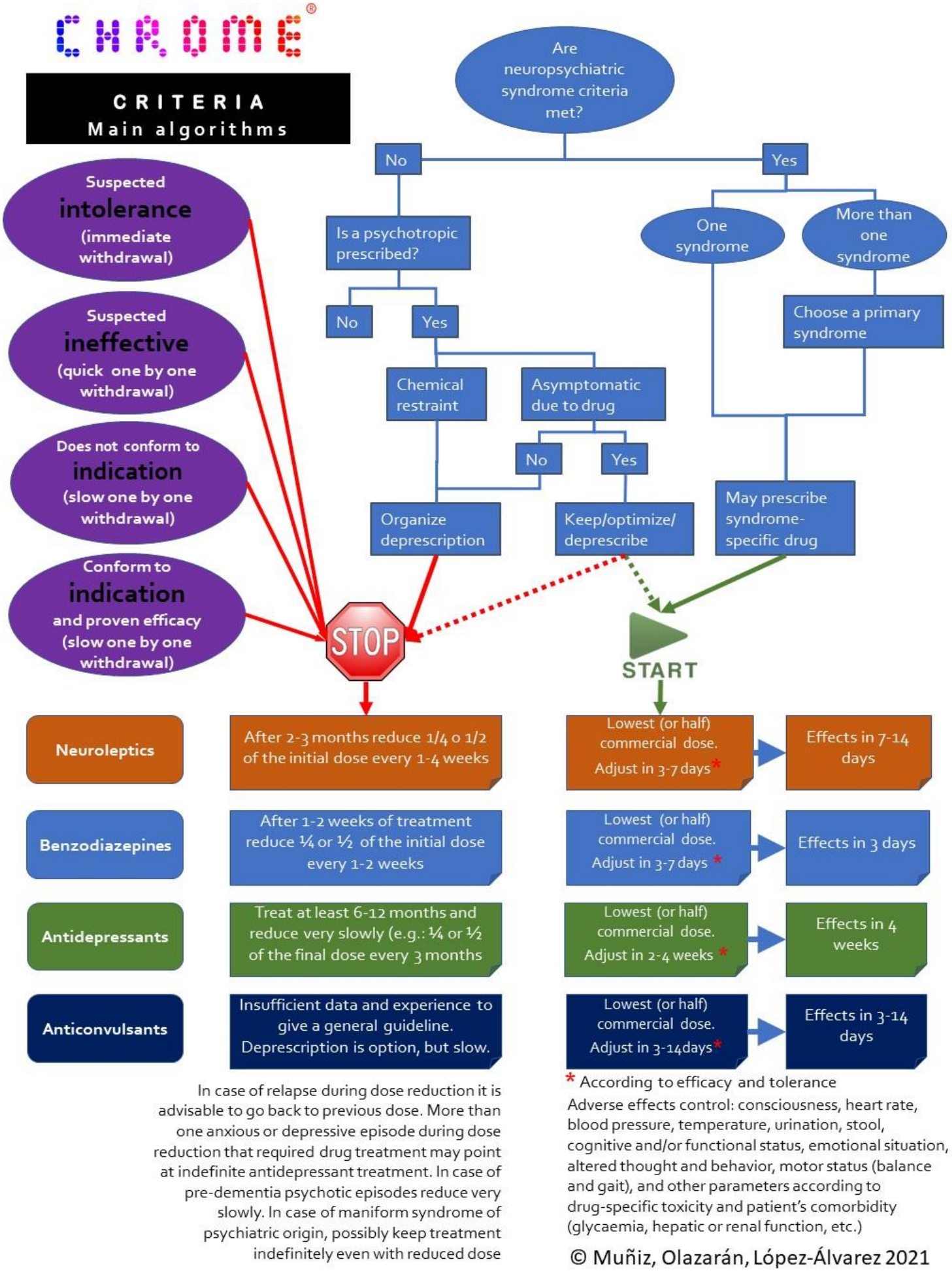

Fig. 1. Algorithm for psychotropic medication withdrawal, initiation, and effect control, according to CHROME criteria.

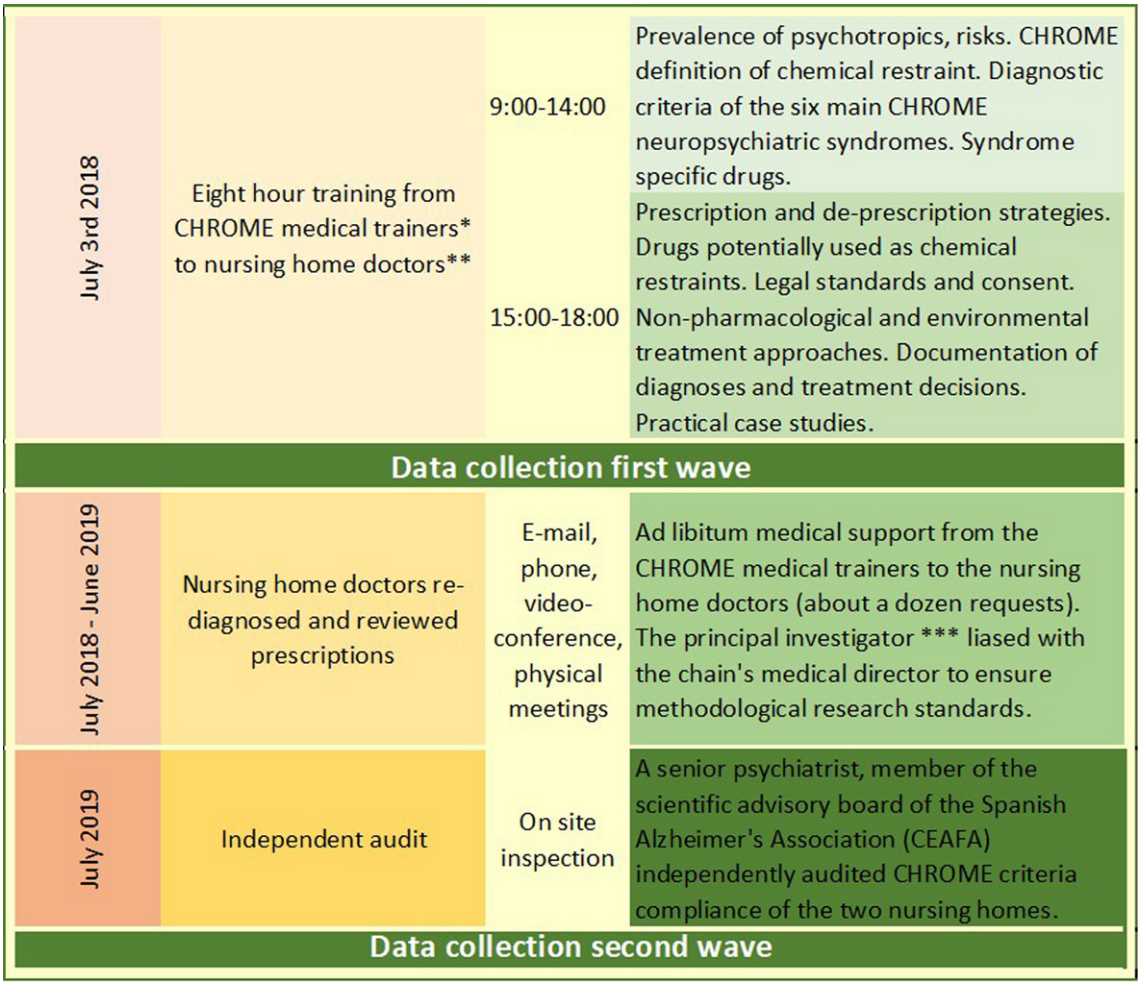

Fig. 2. Study design, time-schedule, and intervention contents. *CHROME medical trainers: JO and JLA; **nursing home doctors: LP, SR, and LG; ***principal investigator: RM; medical director: LP; study director: JO.

and certified by an external auditor of the Spanish Alzheimer's Society (CEAFA) as compliant with all CHROME criteria. Data were collected at two points in time (study waves), i.e., July 2018 and July 2019. Written informed consent for study participation was obtained from capable patients, according to the medical doctors criterium; otherwise, consent was provided by the patients' legal representatives. Ethics committee consultation was not deemed necessary because CHROME implementation follows the standards of medical treatment and care.

As CHROME criteria are specific for cognitive deterioration, participants were all residents with a score ≥ 3 in the Global Deterioration Scale (GDS) [36]. The first study wave (July 2018) reports the situation of the nursing homes right after only medical doctors received CHROME training. The two facilities employed three full-time medical doctors (LP, SR, and LG), LP being at that time also home administrator and medical director of the entire chain. The study director (JO) and the principal investigator (RM) ensured that LP had no influence on diagnoses or prescriptions of the other physicians. The second wave shows the data right after both homes passed the external audit (July 2019), performed by a senior psychiatrist.

Training of eight hours was provided to the medical doctors by the Maria Wolff medical trainers (JO, JLA), including CHROME neuropsychiatric syndrome diagnosis, characteristics of drugs applicable to each syndrome, and deprescribing strategies, among other contents (Fig. 2 and Supplementary Material 2). Medical doctors could contact their

trainers over the entire 12-month intervention period, on an as-needed basis.

To differentiate symptom-based pre-intervention diagnoses from post-intervention CHROME syndromic diagnoses, we called the former "diagnostic impressions" and the latter "CHROME diagnoses". Medical doctors were asked to document their diagnostic impressions on a spreadsheet right after the initial training (July 2018). Over the ensuing months doctors got fully familiarized with CHROME syndrome-based diagnoses, which were documented as post-intervention CHROME diagnoses. The frequencies of those diagnostic impressions were recorded, together with CHROME diagnoses and all other scales reported below.

After first-wave data were recorded, doctors reviewed the diagnoses of patients on a one-by-one basis. Special emphasis was made to review usual overdiagnosis. Overdiagnosis ensues out of a) confusing symptoms with syndromes, b) inherited diagnoses or treatments of physicians no longer in charge of the residents, c) exaggerated symptom reports/perceptions, or d) relatives or co-workers pressuring for sedation out of convenience or ill understood humanity. Some of these prescribing practices are clear chemical restraints [11].

In case of two or more previously diagnosed concurrent syndromes, or clinical overlap between syndromes, physicians tried to identify a single underlying primary syndrome. This led to many residents, previously diagnosed with two or even three diagnoses and their corresponding drugs, to be diagnosed usually with only one or even no neuropsychiatric syndrome. Besides facilitating significant deprescribing, this procedure allowed "certain" or "possible" chemical restraints to be identified and eliminated (see Supplementary Table 1 for chemical restraint criteria). Drugs were then accordingly deprescribed. Once all residents' diagnoses were reassessed and prescriptions reviewed according to CHROME guidelines and standards, the audit was performed in both homes. Post-audit data are shown in the July 2019 wave.

Psychotropic medications were divided according to the following categories: antidepressants, atypical neuroleptics, typical neuroleptics, short/medium half-life benzodiazepines (BZD), long half-life benzodiazepines, other hypnotics/sedatives, antiepileptic medications, cholinesterase inhibitors (CEI), and memantine. Psychotropic prescription was coded as present or not, regardless of its intentional use (pain, epilepsy, etc.), either continuous or PRN prescription, in the previous week to the study wave.

Quality of life was measured using the revised version of the Alzheimer's Disease-Related Quality of Life scale (ADRQL) [37]. This instrument, which is answered by a close caregiver, measures QoL in five domains using a 0–100 scale. The use of a proxy, as well as the modest correlations of ADRQL scores with cognitive and functional disability, renders this instrument particularly well-suited for the study of QoL in people with advanced dementia.

In addition, the following secondary outcome measures were obtained:

- Performance of activities of daily living (ADL), according to the Functional Assessment Staging (FAST) [38]. The FAST evaluates functional dependence when secondary to cognitive deterioration and classifies patients according to seven principal levels of dependence. Since sub-scores are provided for some of those levels, a final score from 1 (no subjective or objective difficulty, FAST 1) to 16 (loss of ability to hold up head independently, FAST 7f) was obtained.
- Basic ADL, according to the Barthel Index [39]. This informant-based scale evaluates performance of 10 basic ADL with global score from 0 (total dependence) to 100 (independence).
- Cognitive performance, measured with the *Mini-Examen Cognoscitivo* (MEC) [40]. The MEC is a Spanish adaptation of Folstein's Mini-Mental State, with possible scores between 0 (worst cognitive performance) and 35 (best cognitive performance).
- Dementia severity, according to the GDS [36]. Based on caregiver interview and patient examination, this scale grades dementia severity from 1 (no dementia symptoms) to 7 (severe dementia).
- Neuropsychiatric symptoms, according to the abridged version of the Neuropsychiatric Inventory (NPI-Q) [41]. Through interview with an informant, the NPI-Q assesses neuropsychiatric symptoms, yielding scores from 0 (no symptoms) to 3 (severe symptoms) for 12 symptom domains (total score ranges from 0 to 36).
- Any type of physical restraint during the last week, at the date of the study wave (excluding side rails).
- Falls accumulated in the six months before the date of the study wave. Four types of falls were separately recorded: non-injurious, with

hip fracture, with other fracture, and with any other complication (e.g., head trauma, cutaneous wound, sprain).
- Referrals to the emergency room six months before the date of the study waves.

The ADRQL and all the secondary outcome measures were administered by qualified home staff, unaware of the study design (these employees performed those and other evaluations in their usual practice). The nursing home doctors provided neuropsychiatric diagnoses, according to the CHROME criteria [11].

Data regarding demographics and prescriptions were extracted from the IT Home Management Database/Software (ResiPlus® - ADD Informática, Torrent, Valencia). Although the evaluators cannot be considered blind, the external audit included more than 20% of cases being randomly selected and verified. No major discrepancies were found between the auditor and the three physicians: neither in diagnoses, nor in treatment adequacy. RM and LP reviewed data base consistency and accuracy at several checkup points.

Demographic and clinical variables were presented using indexes of frequency, central tendency, and dispersion. Confidence intervals were obtained for the categorical variables in the total sample and Wilcoxon test was utilized to analyze the evolution of the subjects that were evaluated at both study waves (completer subjects). Increase in confidence of neuropsychiatric diagnosis after full CHROME training was analyzed using the certainty increase ratio (CIR), defined as the odds ratio of certain versus possible diagnosis at the second wave measurement, in comparison with first-wave diagnostic impression.

The primary analysis was pre-post comparison of frequencies of psychotropic prescribing and QoL measurements. Assuming type I error of 0.05 and type II error of 0.80 and using the data obtained in the first wave, the study was powered to detect absolute reductions of 14.9%, 15.0%, and 10.7% in, respectively, antidepressant, atypical neuroleptic, and antiepileptic medications (total sample), as well as to detect a change of 3.3 points (effect size of 0.19) in the ADRQL total score (completer subjects). Since high interdependence between the different measures of effect was expected, multiple comparisons were controlled using the method of false discovery rate (FDR). As we conducted 28 effect comparisons, the level for statistical significance was set at $p < 0.026$ [42]. The statistical analyses were performed using the Statistical Package for Social Sciences version 15.0 software (SPSS, Chicago, IL).

RESULTS

A total of 171 residents were included in the study. They were predominantly women (78.9%) with a mean age (SD) of 87.8 (5.7). Mean (SD) number of medications was 7.8 (3.7) at study inclusion and 32.2% of the residents had some type of physical restraint. Severity of dementia was as follows: 15.2% mild cognitive impairment, 16.4% mild dementia, 21.1% moderate, 30.4% moderately severe, and 17.0% severe dementia.

The total sample consisted of 147 residents present in the first wave and 139 residents present a year later in the second wave (differences in numbers due to death [$n = 22$], leaving the home [$n = 10$], and new residents [$n = 24$]). Hence, the sub-sample of residents present at both waves was 115 (completer subjects). Demographic characteristics and study variables of the total sample and the completer subjects are presented in Table 2. The mean (SD) number of psychotropic prescriptions was reduced from 1.9 (1.1) to 0.9 (1.0), which represents an absolute reduction of one medication per patient and a relative reduction of 52.6%. The drugs most reduced in absolute terms were antidepressants (76.9% pre-intervention, 33.8% post-intervention) and atypical neuroleptics (38.8% pre-intervention, 15.1% post-intervention), but remarkable relative reductions of 87.0% and 65.0% were also achieved for, respectively, short/medium half-life and long half-life benzodiazepines (total sample).

Response to surroundings displayed marked improvement from the first to the second measurement (pre-intervention mean value [SD] 72.1 [30.2], post-intervention mean value [SD] 82.3 [27.9], $p < 0.0005$), but social interaction deteriorated slightly (pre-intervention 73.3 [26.3], post-intervention 69.2 [28.4], $p = 0.012$). A trend of improvement in feelings and mood was observed ($p = 0.037$), while the QoL total score was not significantly changed ($p = 0.541$). There was mild improvement in NPS (pre-intervention 2.5 [3.1], post-intervention 2.1 [2.5], $p = 0.008$) and a trend of less emergency room referrals was also reported ($p = 0.093$). No significant differences or trends were observed in the occurrence of falls or restraints (Table 2).

A high frequency of diagnostic impressions was given in the first wave, particularly for sleep

Table 2
Demographic and clinical variables at both study waves

	Total sample		Completer residents		p^5
	July, 2018 (pre-CHROME) ($n = 147$)	July, 2019 (post-CHROME) ($n = 139$)	July, 2018 (post-CHROME) ($n = 115$)	July, 2019 (post-CHROME) ($n = 115$)	
Age	87.8 (6.0)	88.1 (5.6)	88.1 (5.9)	89.1 (5.9)	NA
Sex (% female)	81.0 (74.6–87.3)	80.6 (74.0–87.2)	83.5 (76.7–90.3)	83.5 (76.7–90.3)	NA
ADL performance (FAST)	7.7 (3.6)	8.6 (3.8)	7.7 (3.7)	8.7 (3.7)	0.000
Basic ADL (BI)	34.7 (29.1)	33.7 (29.6)	36.8 (29.9)	32.2 (28.7)	0.003
Cognition (MEC)	12.7 (9.7)	11.6 (9.3)	13.0 (9.7)	10.8 (9.2)	0.000
Dementia severity (GDS)	5.1 (1.5)	5.4 (1.4)	5.1 (1.4)	5.5 (1.4)	0.000
Neuropsychiatric symptoms (NPI-Q)	2.5 (2.9)	2.1 (2.6)	2.5 (3.1)	2.1 (2.5)	0.008
Total medications (*n*)	7.8 (3.7)	6.6 (3.5)	7.7 (3.5)	6.5 (3.4)	0.000
Psychotropic medications (*n*)[1]	1.9 (1.1)	0.9 (1.0)	1.9 (1.1)	0.8 (1.0)	0.000
Antidepressants (%)	76.9 (70.1–83.7)	33.8 (25.9–41.7)	79.1 (71.7–86.6)	32.2 (23.6–40.7)	0.000
Atypical neuroleptics (%)	38.8 (30.9–46.7)	15.1 (9.2–21.1)	40.0 (31.0–49.0)	16.5 (9.7–23.3)	0.000
Typical neuroleptics (%)	0.0	0.7 (0.0–2.1)	0.0	0.9 (0.0–2.6)	0.319
Short/medium half-life BZD (%)	5.4 (1.8–9.1)	0.7 (0.0–2.1)	4.3 (0.6–8.1)	0.9 (0.0–2.6)	0.045
Long half-life BZD (%)	2.0 (0.0–4.3)	0.7 (0.0–2.1)	1.7 (0.0–4.1)	0.0	0.158
Other hypnotics/sedatives (%)	8.8 (4.3–13.4)	11.5 (6.2–16.8)	7.0 (2.3–11.6)	9.6 (4.2–14.9)	0.259
Antiepileptic medications (%)	17.7 (11.5–23.9)	13.7 (8.0–19.4)	17.4 (10.5–24.3)	13.9 (7.6–20.2)	0.207
Dementia medications (%)[2]	21.1 (14.8–30.0)	17.2 (11.2–23.3)	22.6 (15.4–29.8)	19.1 (12.2–26.0)	0.341
Physical restraint (%)[3]	34.5 (26.7–42.2)	27.3 (19.9–34.7)	31.9 (23.3–40.4)	28.7 (20.4–37.0)	0.408
Double bed rail (%)	52.4 (44.3–60.5)	49.6 (41.3–58.0)	49.6 (40.3–58.8)	48.7 (39.6–57.8)	0.783
Non-injurious fall (%)[4]	50.3 (42.3–58.7)	47.8 (39.2–55.8)	47.8 (38.7–57.0)	53.9 (44.8–63.0)	0.286
Fall with hip fracture (%)[4]	1.4 (0.0–3.2)	4.3 (0.9–7.7)	1.7 (0.0–4.1)	3.5 (0.1–6.8)	0.414
Fall with other fracture (%)[4]	2.0 (0.0–4.3)	2.2 (0.0–4.6)	2.6 (0.0–5.5)	2.6 (0.0–5.5)	1.000
Fall with other complication (%)[4]	2.0 (0.0–4.3)	1.4 (0.0–3.4)	1.7 (0.0)	1.7 (4.1)	1.000
Emergency room referral (%)[4]	45.6 (37.5–53.6)	32.4 (24.6–40.2)	41.7 (32.7–50.8)	32.2 (23.6–40.7)	0.093
Quality of life (ADRQL)					
Social interaction	71.8 (26.9)	70.9 (27.8)	73.3 (26.3)	69.2 (28.4)	0.012
Awareness of self	49.1 (26.6)	50.2 (28.4)	49.1 (26.2)	48.5 (29.1)	0.541
Feelings and mood	74.0 (25.2)	79.9 (22.7)	73.6 (25.3)	78.5 (23.1)	0.037
Enjoyment of activities	52.2 (34.5)	49.8 (38.5)	50.8 (35.0)	47.7 (38.8)	0.247
Response to surroundings	70.9 (31.3)	84.1 (26.8)	72.1 (30.2)	82.3 (27.9)	0.000
Total score	66.0 (18.7)	68.7 (20.4)	66.3 (18.4)	67.1 (20.8)	0.541

Figures represent mean value (SD) or percentage (95% confidence interval). [1]CEI and memantine were not included; [2]CEI and/or memantine; [3]bed rails were not included; [4]residents with at least one event; [5]Wilcoxon test for the completer group. ADL, activities of daily living; BI, Barthel Index; ADRQL, Alzheimer's Disease-Related Quality of Life (0 worst, 100 best score); BI, Barthel Index (0 worst, 100 best score); BZD, benzodiazepines; CEI, cholinesterase inhibitors; CHROME, Chemical Restraints Avoidance Methodology; FAST, Functional Assessment Staging (1 best, 7 worst score); GDS, Global Deterioration Scale (1 best, 7 worst score); MEC, *Mini-Examen Cognoscitivo* (0 worst, 35 best score); NA, not applicable; NPI, Neuropsychiatric Inventory, abridged version (0 best, 36 worst score).

disturbance (61.2%), anxiety (60.5%), depression (57.8%), and psychotic syndrome (38.1%), which were significantly reduced after reviewing patients according to CHROME's diagnostic criteria of neuropsychiatric syndromes (the respective frequencies being 33.1%, 37.4%, 30.9%, and 20.1%, total sample). The highest absolute reduction (28.1%) was observed for sleep disturbance, while maximal relative reduction (47.2%) was noted for impulsive and psychotic syndromes. The use of CHROME criteria only increased the diagnostic certainty for the impulsive syndrome (Table 3).

Positive subjective experiences were spontaneously communicated by the medical doctors during the intervention period. Patients were seemingly more aware, and the home's atmosphere had reportedly changed for the better. Moreover, nurses and nurse aides manifested to prefer working with more responsive residents.

DISCUSSION

The CHROME criteria were applied on a sample of very aged, fragile subjects, with a high frequency of psychotropic prescription, particularly for antidepressants and neuroleptics (Table 2). Sleep disturbance, anxiety, and depression were highly identified based on physicians' first diagnostic impressions. However, the frequency of those labels

Table 3
Description of neuropsychiatric impressions and CHROME diagnoses

	Total sample		Completer residents		
	July, 2018 ($n = 147$) Diagnostic impression	July, 2019 ($n = 139$) CHROME diagnosis	July, 2018 ($n = 115$) Diagnostic impression	July, 2019 ($n = 115$) CHROME diagnosis	p^1
Depression					
Possible	22.4	7.9	22.6	8.7	
Certain	35.4	23.0	35.7	19.1	
Total	57.8 (49.8–65.8)	30.9 (23.3–38.6)	58.3 (49.2–67.3)	27.8 (19.6–36.0)	0.000
CIR		1.84 (0.70–4.84)		1.39 (0.53–3.63)	
Anxiety					
Possible	16.3	12.2	17.4	12.2	
Certain	44.2	25.2	44.3	22.6	
Total	60.5 (52.6–68.4)	37.4 (29.4–45.5)	61.7 (52.9–70.6)	34.8 (26.1–43.5)	0.000
CIR		0.76 (0.31–1.85)		0.73 (0.30–1.77)	
Psychotic syndrome					
Possible	12.2	9.4	11.3	10.4	
Certain	25.9	10.8	27.0	12.2	
Total	38.1 (30.2–45.9)	20.1 (13.5–26.8)	38.3 (29.4–47.1)	22.6 (15.0–30.3)	0.000
CIR		0.54 (0.18–1.64)		0.49 (0.17–1.45)	
Impulsive syndrome					
Possible	15.6	1.4	13.9	1.7	
Certain	6.1	10.1	5.2	10.4	
Total	21.8 (15.1–28.4)	11.5 (6.2–16.8)	19.1 (11.9–26.3)	12.2 (6.2–18.2)	0.033
CIR		18.45 (2.50–136.34)		16.35 (2.42–110.32)	
Maniform syndrome					
Possible	0.7	0.7	0.9	0.0	
Certain	0.0	0.7	0.0	0.9	
Total	0.7 (0.0–2.0)	1.4 (0.0–3.4)	0.9 (0.0–2.6)	0.9 (0.0–2.6)	1.000
CIR		NA		NA	
Sleep disturbance					
Possible	17.0	11.5	17.4	12.2	
Certain	44.2	21.6	41.7	18.3	
Total	61.2 (53.3–69.1)	33.1 (25.3–40.9)	59.1 (50.1–68.1)	30.4 (22.0–38.8)	0.000
CIR		0.72 (0.29–1.79)		0.63 (0.25–1.56)	

Figures represent frequency (95% confidence interval), except for the CIR, which is expressed as odds ratio. CIR, certainty increase ratio (odds ratio of certain versus possible diagnosis); NA, not applicable; [1]Wilcoxon test for the completer group.

dropped drastically after being reviewed by the stringently defined neuropsychiatric syndromes of the CHROME criteria and, consequently, psychotropic prescriptions were reduced (Tables 2 and 3).

Syndromic diagnoses and prescriptions were similar among both the completer and the total study samples, indicating successful application of the CHROME criteria, even in patients admitted to the nursing home during the study period whose medical history was often patchy, or unavailable.

Despite achieving important reduction of psychotropic prescribing, no drug category was completely deprescribed. These results are consistent with CHROME's focus on treatment optimization, rather than exclusively deprescribing, thus allowing a subset of residents on medication, including neuroleptics, the most dangerous group. According to the present and previous studies, neuroleptic treatment may be indicated in 10–20% of institutionalized people with dementia [11, 27, 43, 44].

No significant changes were detected in total QoL after implementing CHROME criteria. One domain, however, improved (response to surroundings), while other (social interaction) slightly deteriorated (Table 2). Previous studies of natural evolution of QoL in institutionalized people with dementia yielded small increase, small decrease, or stabilization in mean QoL scores, but high interindividual variability was reported. The only study describing one-year evolution in the ADRQL reported significant improvement in feelings and mood along with trend of improvement in response to surroundings, which is quite consistent with our results, but deterioration in social interaction was not observed [45]. Worsening of social interaction in our residents could be caused by increased apathy, as severity of dementia

advanced [46], while improvement in response to surroundings could result out of increased adequacy of psychotropic prescriptions (in fact: the response to surroundings items of the ADRQL mainly reflect anxiety- and depression-related behaviors).

Very few studies of interventions aimed at reducing or optimizing psychotropic medications reported QoL outcomes. Using the Beer's criteria [21], potentially harmful medications were identified by trained nurses in a randomized controlled trial including 227 elderly residents (93% dementia) from assisted living facilities. Psychotropic prescription was significantly reduced in the intervention group and there was a decline in QoL in both the intervention and control groups, although the decline was significantly lower in the intervention group. In addition, difference in hospitalization was observed in favor of the intervention group [47].

An educational deprescribing program focused on nonpharmacological prevention and management of behavioral and psychological symptoms of dementia (BPSD) was implemented and evaluated in 139 residents (98% dementia) from 23 nursing homes, taking regular antipsychotic medication for at least three months. Neuroleptic reduction of 82% was achieved, without change in BPSD or adverse outcomes [48].

In apparent contrast to our findings is a study that reports worsening of NPS after reducing antipsychotics which were compensated for in a psychosocial intervention group [43]. The worsening of symptoms could be due to better adequacy in neuroleptic prescription, since there was an 18% initial frequency of prescription, compared to 39% in our study. In another trial, the initial frequency of neuroleptic prescription (9%) remained stable throughout the follow-up, while QoL and NPS improved after psychosocial intervention [26].

In our sample, possible changing needs of patients due to drug reviews were spontaneously absorbed by "usual care". It must be noted that the philosophy of the Albertia chain is to engage in non-pharmacological treatment methods and staff training on an ongoing basis. Several psychosocial programs had been implemented and integrated by the homes before implementing the CHROME criteria as "usual care". At the time of the review of prescriptions, no special efforts were made by non-medical staff.

The present investigation had several limitations to be noted. The naturalistic, observational study design precluded attribution of QoL changes to CHROME intervention, although lack of overall negative effect could be reasonably demonstrated. The study's primary and secondary outcome measures were recorded by personnel that routinely performed those evaluations for clinical follow-up of residents. Although blinded to the study's goals and methodology, they did not strictly qualify as blind raters. In addition, overall prescribing was reduced, but prescription switch and medication dose, which could have influenced mood, behavior, and QoL, were not analyzed. As for effect measurement, future studies should include qualitative research methods to evaluate the subjective impact of CHROME implementation, since staff reports point in a better direction than the quantitative measures of QoL or NPS.

Implementing CHROME criteria without an external audit in view might produce unsystematic use (cherry-picking only certain components) and not deliver the results shown here. Integrating CHROME criteria in a home's everyday practice requires some learning. Teaching materials have been simplified and schematized (see Table 1, Fig. 1, and Supplementary Material) since the implementation reported herein.

In conclusion, CHROME criteria offer practical solutions for issues faced by many non-specialized clinicians relative to psychopharmacological treatment of behavioral and psychological issues of people with dementia. Treatment is organized around six neuropsychiatric syndromes instead of BPSD. Focus is on treatment optimization (psychotropics, medical, environmental, and non-pharmacological), and not merely on drug elimination. Nonetheless, significant reductions occurred in most drug categories, not just antipsychotics. QoL was slightly improved, and no adverse events were identified. Diagnostic criteria, treatment guidelines, chemical restraint definition, legal issues, pharmaceutical best practices, and auditing methods are summarized. Implementation is easy and beneficial for people with dementia.

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CONFLICT OF INTEREST

JO and JLA received honoraria from Albertia for their training services outside of this study; LP, SR and LG are employed at Albertia.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/ADR-210015.

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Supplementary Material

CHROME Criteria and Quality of Life: A Pilot Study from Maria Wolff-Albertia

Supplementary Material 1

The CHROME criteria for quality prescribing of psychotropic medications in institutionalized people with dementia

(updated on December 2020)

1. Definition of chemical restraint

Chemical restraint is defined as a psychoactive drug that is prescribed:

a) not complying with any of the six neuropsychiatric syndromes defined by the CHROME criteria or
b) for organizational convenience

Some examples of chemical restraints are: prescriptions to suppress or reduce “demanding behaviors, like seeking constant “attention or care”, “screaming”, “singing”, “behaviors that can give a bad impression to visitors”, induce patients to extend their stay in bed, treat unspecific "agitation", wandering, etc.

2. Neuropsychiatric syndromes: key to quality prescription of psychotropics

Neuropsychiatric syndromes define clinical pictures of persistent and significant discomfort or risk that arises from a pathological substrate (anatomical/chemical) and are not mere consequences of the environment.

Another condition for symptoms to be included under the umbrella of neuropsychiatric syndromes, in dementia, is that cognitive impairment cannot fully explain these.

The CHROME criteria’s proposal is to prescribe based on strict compliance with six dementia-relevant neuropsychiatric syndromes. This syndromic prescription approach should improve prescription quality if compared to those based on behavioral and psychological symptoms of dementia (BPSD). Prescriptions on a BPSD basis have to date, produced no prescription agreements. This may be because many underlying pathologies can cause these symptoms. Instead, the neuropsychiatric approach proposes to target (as far as possible) the underlying pathology of symptoms. Environmental, and non-pharmacological approaches remain first choices.

Supplementary Table 1 summarizes the definitions of relevant neuropsychiatric syndromes, developed by the CHROME expert panel.

3. Check-list before prescribing pharmacological treatment

The following issues should be considered once the manifestation or target symptom has been identified and before starting pharmacological treatment:

- Is it an adaptive phenomenon that will tend to fade once the environmental cause disappears?
- Has an organic cause, other than dementia, been ruled out (e.g., pain, infection ...)?
- May non-pharmacological measures and/or adjustment of the current medication be enough?
- Have dementia medications (i.e., cholinesterase inhibitors and memantine) been optimized?
- Is it a pathological phenomenon susceptible to specific pharmacological treatment effective beyond sedation (i.e., neuropsychiatric syndrome)?
- Do the short, medium, and long-term benefits of pharmacological treatment exceed the inherent risks of the medication to be used?

The suitable medications for the different neuropsychiatric syndromes, according to the existing literature and CHROME expert opinion (evidence level C) are presented in Supplementary Table 2.

4. Accreditation of chemical restraint free facilities

As CHROME criteria are designed to allow external diagnostic audit (physician), nursing homes, or similar facilities can be evaluated for compliance.

The accreditation process consists of four phases:

a) Training (If needed)
b) Implementation and consultancy (If needed)
c) External auditing/verification
d) Final report and accreditation (if requirements are met)

Training, implementation, and consultancy phases include exchange of information between the home's medical and other staff and the CHROME criteria consultants. In addition, the CHROME experts implement a consultancy program to facilitate the organization of all involved departments.

The audit checks on site for:

a) Quality prescription of psychoactive drugs in accordance to the CHROME criteria, and therefore:
b) If chemical restraints are present or not
c) Compliance with minimum legal standards of psychotropic prescriptions
d) Compliance with pharmacy standards (drug acquisition, storage, administration, and disposal)

The methodology and steps of the auditing/verification phase are the following:

- The physician to conduct the audit is external (e.g., hired by the National Alzheimer's Society), very experienced in BPSD treatment, as well as previously trained by the CHROME criteria panel experts
- Identification of all the residents of the facility with dementia
- Random selection of 20% of residents with dementia for verification, as well as:
- Selection of all residents receiving more than three psychotropic drugs
- The auditing physician, accompanied by the center physician, evaluates the information available in the medical records of the selected residents and explores these residents where they usually live
- In addition, the auditing doctor may spontaneously select any resident which, by reason of his or her appearance, might be at risk of chemical restraint (residents looking bloated, claiming attention, being restless, etc.)
- The auditor assesses aspects which will be individually verified and introduced systematically on the assessment sheets: diagnosis of dementia, prescription of drugs for BPSD, informed consent, initial adjustment of the prescription, response to the drug, control of possible adverse effects, current dose, and adequacy of maintaining prescription and dose
- Patients' legal right for a written informed consent are checked for in those few cases where prescriptions imply a known important risk. For lower risk prescriptions verbal informed consent suffices but must always be recorded.
- Finally, the auditor examines the entire logistical chain of acquisition, storage, dispensation, and disposal of all psychotropic medications of the facility. Compliance with local legal norms are checked for, as well possible deficiencies in the process that might make unlawful use psychotropics possible.

The verification phase ends with the completion of a report by the auditing physician, which is written outside the premises. The report includes suggestions for improvement and whether the "accreditation of chemical restraint free center" can or cannot be granted.

The audit(or) distinguishes between "definitive" and "possible" chemical restraints, which are defined in Table 3. The accreditation of "chemical restraint free facility" is only granted if there is less than one definitive chemical restraint and less than three possible chemical restraints for every 100 people with dementia in the center.

Addendum

List of medications to be considered as potential chemical restraints

1. Neuroleptics

a) Typical neuroleptics. Amisulpiride (Aracalm, Solian), clorpromazine (Largactil), clotiapine (Etumine, Etumina), droperidol (Xomolix), flufenazine (Modecate), haloperidol*, levomepromazine (Sinogan), loxapine (Adasuve), perfenazine (Decentan), periciazine (Nemactil), pimozide (Orap), pipotiazine (Piportil), sulpiride (Ansium+, Dogmatil, Psicocen, Tepazepan+), tiapride (Tiaprizal), tiotixene (Navane), trifluoperazine (Stelazine), trifluoperidol (Psicoperidol), zuclopentixol (Clopixol)
b) Atypical neuroleptics. Asenapine (Sycrest), clozapine (Clozabrain, Leponex, Nemea), flupentixol (Deanxit+), paliperidone (Xeplion), risperidone* (Arketin, Calmapride, Diaforin,

Rispemylan, Risperdal), quetiapine* (Psicotric, Qudix, Quentiax, Rocoz, Seroquel), olanzapine (Arenbil, Zalasta, Zolafren, Zyprexa, Zypadhera), paliperidone (Invega, Xeplion), sertindol (Serdolect), ziprasidone (Zeldox, Zypsilan)

c) Third generation neuroleptics. Aripiprazole (Abilify, Apaloz, Arizol)

2. Benzodiazepines

a) Short/intermediate half-life benzodiazepines. Alprazolam* (Trankimazin), bentazepam (Tiadipona), brotizolam (Sintonal), clotiazepam (Distensan), loprazolam (Somnovit), lorazepam* (Orfidal, Placinoral), lormetacepam* (Aldosomnil, Loramet, Noctamid), midazolam (Buccolam, Dormicum), triazolam (Halcion)

b) Long half-life benzodiazepines. Bromazepam* (Lexatin), clobazam (Noiafren), clonazepam (Rivotril), clorazepate* (Tranxilium), chlordiazepoxide (Huberplex), diazepam* (Aneurol+, Stesolid, Tropargal+, Valium), flurazepam (Dormodor), ketazolam (Sedotime), medazepam (Nobritol+), pinazepam (Duna), quazepam (Quiedorm)

3. Antidepressants

a) Tryciclic and related antidepressants. Amitriptiline (Deprelio, Nobritol+, Tryptizol), clomipramine (Anafranil), doxepine (Sinequan), imipramine (Tofranil), nortriptiline (Paxtibi, Tropargal+), tianeptine (Zinosan), trimipramine (Surmontil), maprotilina (Ludiomil), mianserine (Lantanon), mirtazapine* (Rexer), trazodone* (Deprax)

b) Serotonine/norepinephrine/dopamine uptake inhibitors. Citalopram* (Citalvir, Prisdal, Seregra, Seropram), desvenlafaxine (Pristiq), duloxetine (Cymbalta, Dulotex, Xeristar), escitalopram* (Cipralex, Diprex, Esertia, Heipram), fluoxetine (Adofen, Luramon, Prozac, Reneuron), fluvoxamine (Dumirox), paroxetine (Arapaxel, Daparox, Frosinor, Motivan, Seroxat, Xetin), reboxetine (Irenor, Norebox), sertraline* (Altisben, Aremis, Aserin, Besitran), venlafaxine (Arafaxina, Dislaven, Dobupal, Flaxen, Levest, Vandral, Venlamylan, Venlapine, Zaredrop, Zarelis), vortioxetine (Brintellix).

4. Antiepileptics

Carbamazepine (Tegretol), eslicarbamazepine (Zebinix), stiripentol (Diacomit), ethosuximide (Zarontin), felbamate (Taloxa), phenytoin (Epanutin, Sinergina), phenobarbital (Gardenal, Luminal, Luminaletas), gabapentin* (Neurontin), lacosamide (Vimpat), lamotrigine (Crisomet, Labileno, Lamictal), levetiracetam (Keppra, Laurak, Tirbas), oxcarbamazepine (Trileptal), perampanel (Fycompa), pregabaline (Aciryl, Gatica, Lyrica), primidone (Mysoline), retigabine (Trobalt), rufinamide (Inovelon), sulthiame (Ospolot), tiagabine (Gabitril), topiramate (Acomicil, Fagodol, Topamax, Topibrain), valproate (Depakine), valpromide (Depamide), vigabatrin (Sabrilex), zonisamide (Zonegran).

5. Other hypnotics/sedatives

Chlormetiazole (Distraneurine), doxilamine (Dormidina, Dormiken, Dormirel, Normodorm), zolpidem* (Dalparan, Stilnox), zopiclone (Datolan, Limovan, Siaten, Zopicalma)

*Frequently used medication; +combination of psychotropic medications

Supplementary Table 1.

Definitions of "definitive" and "possible" chemical restraints

DEFINITIVE CHEMICAL RESTRAINT The criteria a, b and c must be fulfilled: a) Any kind of neuropsychiatric syndrome clearly absent b) The drug was clearly prescribed for organizational convenience c) Absence of any ongoing withdrawal plan
POSSIBLE CHEMICAL RESTRAINT At least one of the following criteria is met: a) There is insufficient information regarding the existence of neuropsychiatric syndrome b) There is no clear response to the drug or the balance between response and tolerance is not admissible c) There was acceptable response and tolerance, but withdrawal should have been attempted
The accreditation of "chemical restraint free facility" will only be issued if there is less than one definitive chemical restraint and less than three possible chemical restraints for every 100 people with dementia in the center.

Supplementary Table 2.

Working definitions of the relevant neuropsychiatric syndromes

SYNDROME*	DEFINITION and CAVEATS
Depression	DEFINITION Mood disturbance that manifests itself as sadness, anhedonia, feeling of being a burden or lack of hope, which occurs persistently (most of the time for the last two weeks) and is a change regarding a previous state.
	CAVEATS In patients with advanced dementia or impaired verbal communication, symptoms can be inferred from attitudes (negative, withdrawn, lack of interest) or from body language (appearance of sadness, crying, etc.). The clinical presentation of anergia, lack of interest and reduced enjoyment in the absence of sadness, feelings of uselessness, guilt, hopelessness, or suicidal ideation might instead suggest an apathetic syndrome.
Anxiety	DEFINITION Excessive or unjustified fear or feeling of loss of control, expressed as fear or apprehension about the present or future, somatic complaints (headache, gastric discomfort, urge to urinate, dry mouth, etc.), repetitive thoughts or obsessive behaviors, which occur persistently (most of the time for the last

	two weeks) and produce significant distress or loss of functioning.
	CAVEATS Patients with advanced dementia or impaired verbal communication, symptoms can be inferred from attitudes (distress, shadowing the caregiver, etc.), body language (quick or deep breathing, getting too easily alarmed, sweating, etc.). De novo manifestation of symptoms of anxiety in patients with dementia must not only imply a reevaluation of previous medical processes and drug treatments, but also an organic assessment in search of a possible medical trigger. Therefore, an anxiety syndrome of neuropsychiatric nature is a diagnosis of exclusion.
Psychotic syndrome	DEFINITION False beliefs or stories (ideas of theft, abandonment, prejudice, infidelity, etc.) or false perceptions (visual, auditory or other), which occur persistently (most days for the last seven days) and cause significant suffering or risks, or a loss of functioning.
	CAVEATS Given the potential risks and suffering of a psychotic syndrome, pharmacologic treatment can be justified even if a systemic illness (or another condition different from dementia) is contributing to the symptoms. In these cases, de-prescription must be attempted as soon as the associated process is controlled. The psychotic syndrome tends to grow smaller and disappear as dementia progresses. In patients with advanced dementia, or in those with important verbal communication deficits, the presence of a psychotic syndrome can rarely be proven. False recognitions, if coexistent with anosognosic manifestations are not going to improve with antipsychotics, thus excluding their indication.
Impulsive syndrome	DEFINITION Lack of foresight or social tact in verbal language, body language or other behaviors (e.g., eating) that occurs persistently (most days for the last two weeks) and causes significant suffering or risk, a loss of functioning, dignity, or social rejection.
	CAVEATS Due to the lack of specific pharmacologic treatments (more even than for the previously described syndromes), modification of institutional or family environment must be considered as the primary variable to be modified. Use of medication must be limited to those situations where impulsiveness puts patient, mates or caregivers at risk, or an important loss of dignity.

	Due to its different origin and treatment, a differential diagnosis regarding the maniform syndrome has to be performed.
Maniform syndrome	DEFINITION Elevated mood and perception of one's own capabilities, feeling abnormally energetic, hyperactive, decreased need for rest, impulsiveness, irritability and anger, which occurs persistently (most of the time for the last week), associated with significant risk or a loss of functioning.
	CAVEATS Should be considered in case of patients with a history of bipolar disorder. Even in these patients, there is high likelihood that symptoms have a secondary cause. For this reason, a new organic assessment needs to be made. The neuropsychiatric origin of the maniform syndrome is therefore a diagnosis of exclusion. The maniform syndrome requires drug treatment, which has to be initiated as soon as antidepressive medication (in case of being present) starts to be decreased or withdrawn.
Sleep disturbance	DEFINITION Loss of the physiological sleep-wake cycle (hypersomnia, insomnia, cycle inversion, fragmented sleep, etc.) that occurs persistently (most days) in the last two weeks
	CAVEATS Primary sleep alteration in elderly with dementia is frequent. It is however mandatory to always check for another syndrome to better explain the disturbance; for example: anxiety, depressive or psychotic syndromes. The organizational need to keep patients in bed longer than desired by them or needed for their physiological rhythms can never justify drug treatments.
In order to diagnose any of the syndromes, the disturbances should not be due to a medical condition (infection, pain, anemia, thyroid disorders, etc.), drugs (including excessive psychotropics), caregiver attitude, stressing environment, lack of stimuli, lack of basic needs (social, respect, etc.), critical event (death of a loved one, change of environment, etc.) or a reaction to cognitive impairment. Manifestations of other syndromes can always coexist within the frame of a primary syndrome (e.g., sleep alteration or delusional ideation in case of a patient with primarily a depressive syndrome) "Syndromes" should never be confused with "traits" or "symptoms". Being extremely sad due to the recent passing away of a loved one, or due to being placed in a nursing home are both normal human reactions that as such have no neuropsychiatric origin. Therefore, in principle there is no need for drug treatment. Instead, these conditions usually need compassionate attention in a wider sense.	

Supplementary Table 3

Medications indicated for the different neuropsychiatric syndromes

	First choice	Second choice
Depression	SSRI, SNRI, other antidepressants (mirtazapine, vortioxetine, bupropion)	
Anxiety	SSRI, SNRI, other antidepressants (mirtazapine, trazodone)	Short/middle half-life benzodiazepines; gabapentin, pregabalin; atypical antypsychotics (quetiapine, olanzapine)*
Psychotic syndrome	Atypical antipsychotics	
Impulsive syndrome	Serotoninergic medications (sertraline, citalopram, escitalopram, trazodone)	Antiepileptic drugs (valproate, gabapentin, pregabalin, carbamazepine, oxcarbamazepine, zonisamide), atypical antipsychotics
Maniform syndrome	Antiepileptic drugs (valproate, carbamazepine, oxcarbamazepine, topiramate), atypical antipsychotics (e.g., quetiapine)	Lithium
Sleep disturbance	Short half-life benzodiazepines (lorazepam, lormetazepam), benzodiazepine analogs (zolpidem, zopiclone), other medications (clomethiazole, trazodone, mirtazapine, gabapentin, pregabalin, melatonin), natural products (valeriana, passiflora)	Atypical antipsychotics (quetiapine, olanzapine)

SNRI, Serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; *last choice.

Supplementary Material 2

Training content of the Maria Wolff-Albertia study

(Only for medical doctors, eight hours duration)

Training topic	Content, sources
Prevalence of psychotropics	Several descriptive studies, studies assessing risks associated to psychotropic prescribing, and critical analyses
CHROME definition of chemical restraint	Supplementary Material 1.1
Diagnostic criteria for the six main CHROME neuropsychiatric syndromes	Supplementary Material 1, Supplementary Table 2, and Muñiz et al., 2021 [1]
Characteristics of drugs applicable to each syndrome	Supplementary Table 3
Quality prescription and de-prescription strategies	Figure 1
Drugs potentially used as chemical restraints	Supplementary Material 1 (Addendum)
Minimum legal standards regarding prescription and consent	Olazarán-Rodríguez et al., 2016 [2] (Supplementary Material)
Non-pharmacological and environmental treatment approaches of symptoms and syndromes	IPA BPSD guidelines [3], Olazarán et al., 2010 [4], and other
Documentation of diagnosis and treatment decisions	Olazarán-Rodríguez et al., 2016 [2] (Supplementary Material)
Practical cases	Actual cases of the nursing homes and other paradigmatic cases

In addition to formal training, medical doctors of both homes could contact their medical trainers over the entire intervention year without restriction to discuss any conceptual or

technical issue, difficult cases encountered, or regarding the process of switching to the new prescription paradigm.

Prior to study inception, the study director (RM) trained the homes' nurses, nurse aides, psychologists, occupational therapists, physiotherapists, medical doctors, and middle managers in person-centered care as well as non-pharmacological therapies and strategies to avoid or treat challenging behaviors.

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