Supplementary Material

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), cloiapine (Etumine, Etumina), droperidol (Xomolix), flufenazine (Modecate), haloperidol*, levomepromazine (Sinogan), loxapine (Adasuve), perfenazine (Decentan), perciazone (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 (Clozabraín, Leponex, Nemea), flupentixol (Deanxit+), paliperidone (Xeplion), risperidone* (Arketin, Calmapride, Diaforin,
Rispemylan, Risperdal), quetiapine* (Psicotric, Quidix, Quentix, Rocoz, Seroquel), olanzapine (Arenbil, Zalasta, Zolafrin, Zyprexa, Zypadhera), paliperidone (Invega, Xeplion), sertindol (Serdolect), ziprasidon (Zeldox, Zypsilan)

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

2. Benzodiazepines

a) Short/intermediate half-life benzodiazepines. Alprazolam* (Trankimazin), bortizolam (Sintonal), clontiazepam (Distensan), lorazepam* (Orfidal, Placinoral), midazolam (Buccolam, Dormicum), triazolam (Halcion)

b) Long half-life benzodiazepines. Bromazepam* (Lexatin), clobazam (Noiafren), clonazepam (Rivotril), miazapine* (Tranxilium), diazepam* (Bromazepam, Huberplex), flurazepam (Dormodor), ketazolam (Sedotime), loprazolam (Somnovit), lormetazepam* (Aldosomnil, Loramet, Noctamid), midazolam (Buccolam, Dormicum), triazolam (Halcion)

3. Antidepressants

a) Trycyclic and related antidepressants. Amitriptiline (Deprelio, Nobritol+, Tryptizol), clomipramine (Anafranil), doxepine (Sinequan), imipramine (Tofranil), nortriptiline (Paxtibi, Tropargal+), trimipramine (Surmontil), maprotiline (Ludiomil), mianserin (Lantanon), trimipramine (Surmontil), maprotilina (Ludiomil), mianserin (Lantanon), mirtazapin (Rexer), trazodon* (Deprax)

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

4. Antiepileptics

Carbamazepine (Tegretol), eslicarbazepine (Zebinix), stiripentol (Diaconit), ethosuximide (Zarontin), felbamate (Taloxa), phenytoin (Epanutin, Sinergina), phenobarbital (Gardenal, Luminal, Luminaletas), gabapentin* (Neurontin), lacosamid (Vimpat), lamotrigine (Crisomet, Labileno, Lamictal), levetiracetam (Keppra, Laurak, Tibas), oxcarbamazepine (Trileptal), perampanel (Fycompa), pregabaline (Acetyl, Gatica, Lyrica), primidone (Mysonine), retigabine (Trobalt), rufinamide (Inovelon), sulthiamine (Ospolot), tiagabine (Gabitril), tiopiramate (Acomicil, Fagodol, Topamax, Topibrain), valproate (Depakine), valpromide (Depamid), vigabatrin (Sabrilex), zonisamide (Zonegran).

5. Other hypnotics/sedatives

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

*Frequently used medication; +combination of psychotropic medications
**Supplementary Table 1.**

**Definitions of “definitive” and “possible” chemical restraints**

| DEFINITIVE CHEMICAL RESTRAINT | POSSIBLE CHEMICAL RESTRAINT |
|-------------------------------|-------------------------------|
| The criteria a, b and c must be fulfilled: | At least one of the following criteria is met: |
| a) Any kind of neuropsychiatric syndrome clearly absent | a) There is insufficient information regarding the existence of neuropsychiatric syndrome |
| b) The drug was clearly prescribed for organizational convenience | b) There is no clear response to the drug or the balance between response and tolerance is not admissible |
| c) Absence of any ongoing withdrawal plan | 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**

| Syndrome                  | 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 antipsychotics (quetiapine, olanzapine) |
| Psychotic syndrome        | Atypical antipsychotics                                                     |                                                                               |
| Impulsive syndrome        | Serotonergic 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.

REFERENCES

[1] Muñiz R, López-Alvarez J, Agüera-Ortiz L, Perea L, Olazarán J (2021) Syndrome-based
prescription to optimize psychotropics: are CHROME criteria a game changer? Front
Psychiatry 12, 662228.

[2] Olazarán-Rodríguez J, López-Álvarez J, Agüera-Ortiz L, López-Arrieta JM, Beltrán-
Aguirre JL, García-García P, Rigueira-García A, Martín-Carrasco M, Quintana-
Hernández D, Muñiz-Schwochert R (2016) [The CHROME criteria for the accreditation
of centers free of chemical restraints and for a quality prescription of psychotropic
medications] Psicogeriatría 6, 91-98. [Article in Spanish]

[3] International Psychogeriatric Association. IPA Complete Guides to Behavioral and
Psychological Symptoms of Dementia (BPSD). https://www.ipa-
online.org/publications/guides-to-bpsd, Accessed June 1, 2021.

[4] Olazarán J, Reisberg B, Clare L, Cruz I, Peña-Casanova J, Del Ser T, Woods B, Beck
C, Auer S, Lai C, Spector A, Fazio S, Bond J, Kivipelto M, Brodaty H, Rojo JM, Collins
H, Teri L, Mittelman M, Orrell M, Feldman HH, Muñiz R (2010) Nonpharmacological
therapies in Alzheimer’s disease: a systematic review of efficacy. Dement Geriatr Cogn
Disord 30, 161-178.