SUPPLEMENTARY MATERIAL

Appendix 1. The CHROME criteria for a quality prescription of psychotropic medications in institutionalized people with dementia

1. Definition of chemical restraint

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

1. not complying with any of the six neuropsychiatric syndromes defined by the CHROME criteria or
2. 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 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.

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 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:

1. Training
2. Implementation and consultancy
3. External auditing/verification
4. 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 the involved departments.

The audit checks on site for:

1. Quality prescription of psychoactive drugs in accordance to the CHROME criteria, and therefore:
2. If chemical restraints are present or not
3. Compliance with minimum legal standards of psychotropic prescriptions
4. 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 (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 those 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

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.

Appendix Table 1. Definitions of “Definitive” and “Possible” chemical restraints

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| Definitive chemical restraint  The criteria a, b and c must be fulfilled:   1. Any kind of neuropsychiatric syndrome clearly absent 2. The drug was clearly prescribed for organizational convenience 3. Absence of any ongoing withdrawal plan |
| POSSIBLE CHEMICAL RESTRAINT  At least one of the following criteria is met:   1. There is insufficient information regarding the existence of neuropsychiatric syndrome 2. There is no clear response to the drug or the balance between response and tolerance is not admissible 3. 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. |

Appendix Table 2. Working definitions of the relevant neuropsychiatric syndromes

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| SYNDROME\* | DEFINITION and CAVEATS |
| Depressive syndrome | 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 at least 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 syndrome | 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 at least 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 at least 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 | 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 at least a 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 alteration | DEFINITION  Loss of the physiological sleep-wake cycle (hypersomnia, insomnia, cycle inversion, fragmented sleep, etc.) that occurs persistently (more than half of the 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 never be entirely be explainable 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. | |

Appendix Table 3. Medications indicated for the different neuropsychiatric syndromes

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|  | First choice | Second choice |
| Depressive syndrome | SSRI, SNRI, other antidepressants (mirtazapine, vortioxetine, bupropion) |  |
| Anxiety syndrome | SSRI, SNRI, other antidepressants (mirtazapine, trazodone) | Short/middle half-life benzodiacepines; 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 alteration | Short half-life benzodiacepines (lorazepam, lormetazepam), benzodiacepine 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