IN THE MIDST OF THE SARS-CoV-2 PANDEMIA, CAUTION IS NEEDED WITH COMMONLY USED DRUGS THAT INCREASE THE RISK OF PNEUMONIA.

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In the present situation of pandemia by SARS-CoV-2, it is imperative to avoid pneumonia/ pneumonitis and related risk factors as much as possible. The consumption of various commonly used medicines increases the risk of and complications from pneumonia.

Medicines can increase the risk of pneumonia or pneumonitis by depressing immunity and other protective mechanisms (e.g., immunosuppressive agents, antipsychotic agents, some opioid analgesics, proton pump inhibitors), by causing sedation, which may increase the risk of aspiration, by depressing pulmonary ventilation and favouring the occurrence of atelectasis (e.g., opioid analgesics, anticholinergic drugs, psychotropic agents), or by a combination of these mechanisms.

The public health impact of the association between exposure to certain drugs and infection or pneumonia depends on the prevalence of use of the concerned drug, the magnitude of the relative risk, and the baseline incidence of the condition (i.e., infection, pneumonia).

Drugs which increase the risk of pneumonia

Antipsychotic drugs(APs)

Antipsychotic agents (aripiprazole, olanzapine, quetiapine, risperidone, haloperidol, among others) are associated with a 1.7 to 3-fold risk of hospitalisation for pneumonia,[1,2,3,4,5,6] and of mortality by pneumonia. As the risk associated with second-generation APs is not lower than that of first-generation agents, sedation and resulting hypoventilation, anticholinergic effects, and their effects on immunity have been proposed as the main mechanisms, rather than their extrapyramidal effects. These drugs however can also cause a respiratory dyskinesia that may be mistaken for asthma or other lung conditions and lead to inappropriate treatment.

In view of the harms induced by the use of antipsychotic agents (APs) for the symptomatic treatment of aggression and psychotic symptoms in elderly patients in residential facilities,[7,8] in 2008 the European national regulatory agencies recommended limiting their use to patients not responding to other interventions, and to reconsider their prescription at every follow up visit, with close patient follow up.[9] In spite of these warnings, APs are widely prescribed off-label to the elderly[10] at inappropriate doses and for too long periods.[11,12,13] In these situations, the harms caused are considerable.[14]International variability in their use[15,16,17,18] is more likely related to variability in off-label use than to variability in the prevalence of mental disorders.

For example, in Catalonia, around 90,000 persons older than 70 receive continued treatment with APs (seven monthly supplies per year). Of those, around 22,000 live in nursing homes. Taking the lowest estimate of relative risk of 1.7, if the annual incidence of pneumonia among the non exposed is 10% in a nursing home, the incidence among those exposed to APs would be 17%, and 70 additional cases of pneumonia attributable to APs would be expected for every

1,000 treated persons (from 100 to 170). For 20,000 exposed persons living in nursing homes, the annual number of additional cases would be 70 x 20 = 1,400.

It is important also to remember that metoclopramide, prochlorperazine and a number of other drugs given for nausea or other gut disturbances are essentially the same drugs as the APs, and can cause tardive and respiratory dyskinesias as well as the other problems linked to these medicines.

Anticholinergic drugs

The consumption of anticholinergic drugs increases the risk of pneumonia by 1.6 to 2.5-fold.[19,20,21]

Various drugs of different therapeutic groups exhibit anticholinergic effects: H1 antihistamines (e.g., chlorphenamine, diphenhydramine, hydroxyzine), antidepressants (e.g., amitryptiline, clomipramine, doxepin, imipramine, paroxetine), urinary antispasmodics (e.g., flavoxate, oxibutinin, tolteridone), gastrointestinal antispasmodics (e.g., dicyclomine), medicines for vertigo (e.g., meclizine, promethazine), antipsychotics (particularly chlorpromazine, clozapine, olanzapine, and quetiapine), antiparkinsonian drugs (e.g., amantadine, biperiden, trihexyphenidil), opioid analgesics, antiepileptic drugs (carbamazepine, oxcarbazepine), and others.

Anticholinergic drugs are commonly prescribed to the elderly. Published estimates of prevalence of use range between 4.3% to more than 20%.[22,23,24,25] The pattern varies from country to country, with codeine plus paracetamol, antidepressants (amitryptiline, dosulepin, paroxetine) and urologicals (predominantly oxibutinin ad tolterodine) generally being those with higher prevalence of use.

Many of these medicines have other mechanisms that can increase sedation and increase the risk of pneumonia in this way. Their anticholinergic effects can add to confusion in someone who may have respiratory compromise and contribute to aspiration in this way. The anticholinergic effect can also contribute to atelectasias in the context of a viral respiratory infection.

Opioid analgesics

Opioid analgesics cause respiratory depression with the resulting pulmonary hypoventilation; some of them (codeine, morphine, fentanyl and methadone) have also immunosuppressive effects. They increase the risk of pneumonia and respiratory mortality by 40% to 75%.[26,27,28]

In 2018, around 50 million persons in the U.S. (15% of U.S. adults, 25% of those older than 65), filled a mean of 3.4 prescriptions for an opioid analgesic, and 10 million persons reported misuse of prescription pain relievers.[29] In Europe in the last years the consumption of mild and strong opioid analgesics has increased, particularly among the elderly.[30,31] Fentanyl and morphine are the most commonly used strong opioids, and more recently oxycodone. Tramadol, which is also a serotonin reuptake inhibitor, is the most commonly used mild opioid. In two recently published observational studies, consumption of tramadol, compared with NSAIDs, was associated with a 1.6-2.6-fold increase in mortality,[32,33] particularly in patients with infection, and in patients with respiratory disease.

Hypnotics and sedatives

Several studies have shown an increase of 20%[34] to 54%[35] in the risk of pneumonia in people consuming hypnotics and sedatives, in particular when they are taken concomitantly with other CNS depressants (e.g., opioids, gabapentinoids).

In the OECD European countries, the national consumption of hypnotics and sedatives shows wide international variability, from 5 DDD per 1,000 inhabitants per day in Austria to 68 in Portugal,[36] and it concentrates in the elderly. In Catalonia, 38% of those older than 70 years consume at least one of these drugs.[37]

Antidepressants

In a cohort study in more than 130,000 patients , a 15% increase of the risk of respiratory-related morbidity and a 26% increase in mortality was seen among older adults with chronic obstructive pulmonary disease (COPD) exposed to SSRI antidepressants.[38] In other studies, an increase in the risk has been seen in patients exposed to antidepressants concomitantly with other CNS depressants.

In part, these findings may stem from extrapyramidal nasopharyngeal disorders these drugs can cause, which lead in 5-10% of patients in clinical trials of a selective serotonin reuptake inhibitor (SSRI) to be diagnosed with nasopharyngitis when in fact these are dystonic effects. In the presence of a coronavirus risk, a misdiagnosis may be problematic.

In the OECD countries, the consumption of antidepressants varies from 11 DDD per 1,000 and per day in Latvia, to 98 in Iceland.[36] In the UK the number of NHS prescriptions for antidepressants doubled between 2008 and 2018.[39]

Gabapentin and pregabalin

In December 2019, the FDA warned about an increased risk of pneumonia and severe respiratory insufficiency and death associated with gabapentinoids, particularly when they are consumed concomitantly with opioid analgesics, hypnotics and sedatives, antidepressants and antihistamines.[40] In 2017 the EMA amended the SPC for gabapentin to include warnings for severe respiratory depression, which may affect up to 1 in 1,000 patients.[41,42]

The summary of product characteristics (SPC) of gabapentin states that the incidence of viral infections in RCTs was "very common" (more than 1 out of 10 treated persons), and that the incidence of pneumonia and of respiratory infection was "common" (between one in 10 and 1 in 100). The SPC of pregabalin warns that in treated patients the incidence of nasopharyngitis is "common" (between 1 in 10 and 1 in 100).[43]

Gabapentin and pregabalin have limited efficacy in the treatment of neuropathic pain, and they are ineffective for their main (off-label) uses in practice, i.e. low back pain with possible radiculopathy.[44,45,46]In spite of this, since 2002 their consumption has more than tripled in the US,[47,48]in the UK[49]and in other European countries,[50,51] often in combination with opioid analgesics and hypnotics.[52]

Proton pump inhibitors (PPIs, omeprazol and analogues)

The reduction of gastric acidity and the increase in gastric and gut bacterial colonization induced by these drugs can also increase the risk of pneumonia. Two meta-analyses of observational studies have shown increases of 34%[53] to 50%.[54] More recent studies have confirmed this magnitude of risk.[55,56,57]

A number of studies have shown a skyrocketing increase in the use of PPIs in the last years. Thirty percent of the population in France,[58] 15% in the UK,[59] 19% in Catalonia,[60] 7% in Denmark,[61] 15% in Iceland,[62] receive PPIs without any apparent justification in one third of cases. It is thus essential to identify patients who do not need these drugs but there is also a need to be aware of a rebound of gastric and anxiety symptoms that can occur on withdrawal.

Cancer chemotherapeutic and immunosuppressive agents

Patients on these drugs are more susceptible to viral and non viral infections, and they should generally not abandon the treatment. However, between 20% and 50% of patients with incurable cancer receive chemotherapy within 30 days of death. In terminally ill cancer patients, the use of palliative chemotherapy a few months before death leads to increased risk of undergoing mechanical ventilation and cardiopulmonary resuscitation and dying in an intensive care unit.[63] In the midst of a COVID-19 pandemia, patients, caregivers and oncologists should have a heightened awareness about the potential risks to them and to others of planning and continuing palliative chemotherapy.

Many patients also receive immunosuppressive agents for inflammatory chronic conditions such as psoriasis, inflammatory bowel disease, or rheumatic arthritis of mild and moderate severity, even though these drugs are only indicated for patients with severe disease not responding to first line treatments. Many of these patients may benefit from stepping down or pausing their treatments for a while and monitoring their clinical state.

Corticosteroids, both systemic, inhaled and occasionally topical or given by eye-drops, have immunosuppressive effects and increase the risk of pneumonia in patients with asthma and in patients with COPD.[64,65] Patients with severe asthma should not abandon corticosteroids, but many patients receive inhaled corticosteroids (ICs) for upper respiratory infections. For example, in Catalonia every year 35,000 children less than 15 years old were prescribed an IC, for occasional apparently unjustified use[66] (except for laryngitis with stridor). Similarly, a proportion of COPD patients do not obtain any benefit from ICs and they can avoid them. In one study, withdrawal of ICs was followed by a 37% decrease in the incidence of pneumonia.[67]

ACE inhibitors (ACEIs) and angiotensin blockers (ARB)

Apart from the debate on a possibly increased risk of complications associated to ACE inhibitors and angiotensin receptor blockers (ARBs),[68,69] a study published in 2012, with 1,039 cases and 2,022 controls, did not find an increased risk of community acquired pneumonia associated to these drugs.[70]

In patients with heart failure, ischaemic heart disease or hypertension, keeping the number of medicines to those necessary and adjusting their treatment accordingly seems more important than withdrawing ACEIs or ARBs.

Ibuprofen or paracetamol for fever?

Given the effects of non-steroidal anti-inflammatory drugs (NSAIDs), it is biologically plausible that respiratory, septic and cardiovascular complications of pneumonia are more frequent and severe if fever is treated with an NSAID instead of paracetamol. An increased incidence of upper and lower respiratory infections associated with NSAIDs has been recorded in randomised clinical trials and in several observational studies,[71] and the summary of product characteristics (SPC) of several NSAIDs warn about them. Such lower respiratory infections are caused by influenza and other viruses (among them common-cold coronaviruses[72]), and NSAIDs may have contributed to many deaths every year worldwide. A strong case has been put forward that an indiscriminate use of high dose aspirin contributed to the mortality of the 1918 influenza pandemic.[73] While doses like this are not used now, this stands as a cautionary tale.

In the absence of specific data regarding COVID-19, paracetamol seems less likely to cause complications.

Concomitant use of various drugs

In modern health care settings, concomitant consumption of several of the drugs mentioned in this report is prevalent, increasing the risk of pneumonia.[74] The concomitant use of multiple drugs, particularly in older populations, has also more generally been linked to increased rates of hospitalisation and an earlier death.[75,76]

In particular, the concomitant consumption of a PPI with one or more psychotropic drugs seems to be highly prevalent in nursing homes,[77] where the risk of contagion and of pneumonia is higher.

Opioids, all antipsychotics, and antidepressants have effects on the heart, as evidenced in lengthening Q-T intervals.[78] Azithromycin and hydroxychloroquine also prolong Q-T intervals and the addition of these drugs to prior treatment may accordingly cause problems.

Conclusions

Several widely used medicines, such as antipsychotics and antidepressants, opioid analgesics, anticholinergic drugs, gabapentinoids, proton pump inhibitors, and inhaled corticosteroids can increase the risk of pneumonia by 1.2 to 2.7 times.

Elderly patients are particularly likely to receive one or more of these drugs. These treatments are often ineffective, and given for unnecessarily long periods, at wrong doses, or for non approved indications.

Although there is wide international variability in the use of these drugs, their prevalence of use in the elderly population is often higher than 10 percent, and sometimes it reaches 40-50 percent. With such a high consumption and a high baseline incidence of viral infection and pneumonia, they can have a significant negative public health impact, and the number of victims can be of the order of hundreds per million inhabitants.

In the present situation of pandemia, unnecessary and harmful treatments should be reviewed and eventually stopped.

- It is urgent to review and in appropriate cases to pause psychotropic drugs (particularly antipsychotics), anticholinergic medicines and opioid analgesics and monitor the effects.
- It is especially important to review the medication burden of residents in nursing homes.
- During the present COVID-19 pandemia, all medications should be critically reviewed and where possible deprescribed, in order to decrease not only the risk of pneumonia and its complications, but also other adverse effects which frequently lead to hospital admission (e.g., fractures).
- We urgently need detailed systematic reviews of clinical trials and observational studies on the association between exposure to drugs and the risk of pneumonia and its complications.
- We also need to establish a collaborative effort in order to support health professionals in adjusting medication burdens to the situation of pandemia, and to develop international collaboration in observational research of risk factors for pneumonia and death by pneumonia.

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[1] Butlletí Groc, 2016. Antipsicóticos: mala ciencia, pseudoinnovación, prescripción desbordada y yatrogenia. https://www.icf.uab.cat/assets/pdf/productes/bg/es/bg293-4.16e.pdf

[2] Trifiró G, Sultana J, Spina E. Are the safety profiles of antipsychotic drugs used in dementia the same? An updated review of observational studies. Drug Safety 2014;37:501-20. doi:https://doi.org/10.1007/s40264-014-0170-y

[3] Knol W, van Marum R, Jansen P, et al. Antipsychotic drug use and risk of pneumonia in elderly people. J Am Geriatr Soc 2008;56:661-66. doi:https://www.ncbi.nlm.nih.gov/pubmed/18266664

[4] Trifiró G, Gambassi G, Sen EF, et al. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: A nested case–control study. Ann Intern Med 2010;152:418-25. doi:10.7326/0003-4819-152-7-201004060-00006. https://annals.org/aim/fullarticle/745702/association-community-acquired-pneumonia-antipsychotic-drug-use-elderly-patients-nested

[5] Mehta S, Pulungan Z, Jones BT, Teigland C. Comparative safety of atypical antipsychotics and the risk of pneumonia in the elderly. Pharmacoepidemiol Drug Safety 2015;24:1271-80. https://doi-org.are.uab.cat/10.1002/pds.3882

[6] Nosè M, Recla E, Trifirò G, Barbui C. Antipsychotic drug exposure and risk of pneumonia: a systematic review and meta-analysis of observational studies. Pharmacoepidemiol Drug Safety 2015;24:812-20. https://onlinelibrary-wiley-com.are.uab.cat/doi/full/10.1002/pds.3804

[7] Schneider LS, Dagerman K, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934-43. https://jamanetwork.com/journals/jama/fullarticle/201714

[8] European Medicines Agency, 2008. CHMP Assessment Report on conventional antipsychotics. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054057.pdf

[9] AEMPS, 2008. Antipsicóticos clásicos y aumento de mortalidad en pacientes ancianos con demencia. Nota Informativa Ref 2008/19. http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2008/docs/NI_2008-19_antipsicoticos.pdf

[10] Oteri A, Mazzaglia G, Pechioli S, et al. Prescribing pattern of antipsychotic drugs during the years 1996–2010: a population based database study in Europe with a focus on torsadogenic drugs. Br J Clin Pharmacol 2016;82:487-97. doi:10.1111/bcp.12955. https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.12955

[11] Gjerden P, Bramness JG, Tvete IF, et al. The antipsychotic agent quetiapine is increasingly not used as such: dispensed prescriptions in Norway 2004–2015. Eur J Clin Pharmacol2017;73:1173-79. doi:10.1007/s00228-017-2281-8. https://link-springer-com.are.uab.cat/article/10.1007/s00228-017-2281-8

[12] Asensio C, Escoda N, Sabaté M, et al. Prevalence of use of antipsychotic drugs in the elderly in Catalonia. Eur J Clin Pharmacol 2018;74:1185-86. https://doi.org/10.1007/s00228-018-2469-6

[13] CatSalut, 2016. Riscos de l'ús de d'antipsicòtics en gent gran. http://medicaments.gencat.cat/ca/professionals/seguretat/fitxes-seguretat/riscos-us-antipsicotics-en-gent-gran/

[14] Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525-38. doi:10.1056/NEJMoa061240 https://www.nejm.org/doi/full/10.1056/NEJMoa061240

[15] Marston L, Nazareth I, Petersen I, et al. Prescribing of antipsychotics in UK primary care: a cohort study. BMJ Open 2014;4:e006135. https://bmjopen.bmj.com/content/4/12/e006135.info

[16] Helvik A-S, Šaltytė Benth J, Wu B, et al. Persistent use of psychotropic drugs in nursing home residents in Norway. BMC Geriatr 2017;17:52. doi:https://doi.org/10.1186/s12877-017-0440-5https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-017-0440-5

[17] Brett J, Karanges EA, Daniels B, et al. Psychotropic medication use in Australia, 2007 to 2015: changes in annual incidence, prevalence and treatment exposure. Aust N Z J Psychiatry 2017;51:990-99. doi:10.1177/0004867417721018. https://doi.org/10.1177/0004867417721018

[18] Montastruc F, Bénard-Laribière A, Noize P, et al. Antipsychotics use: 2006–2013 trends in prevalence and incidence and characterization of users. Eur J Clin Pharmacol 2018;74:619-26. https://doi.org/10.1007/s00228-017-2406-0

[19] Chatterjee S, Carnahan RM, Chen H, et al. Anticholinergic medication use and risk of pneumonia in elderly adults: a nested case–control study. J Am Geriatr Soc 2016;64:394-400. https://doi-org.are.uab.cat/10.1111/jgs.13932

[20] Paul KJ, Walker RL, Dublin S. Anticholinergic medications and risk of community-acquired pneumonia in elderly adults: a population-based case–control study J Am Geriatr Soc 2015;63:476-85. https://doi-org.are.uab.cat/10.1111/jgs.13327

[21] ButlletíGroc, 2005. Riesgos de los fármacos anticolinérgicos en personas de edad avanzada. https://www.icf.uab.cat/assets/pdf/productes/bg/es/bg281.15e.pdf

[22] Lönnroos E, Gnjidic D, Hilmer SN, et al. Drug burden index and hospitalization among community-dwelling older people. Drugs & Aging 2012;29:395-404. doi:10.2165/11631420-000000000-00000.

[23] Herr M, Sirven N, Grondin H, et al. Frailty, polypharmacy, and potentially inappropriate medications in old people: findings in a representative sample of the French population. Eur J Clin Pharmacol 2017;73:1165-72. https://link-springer-com.are.uab.cat/article/10.1007/s00228-017-2276-5

[24] Byrne CJ, Walsh C, Cahir C, et al. Anticholinergic and sedative drug burden in community-dwelling older people: a national database study. BMJ Open2018;8(7):e022500. doi:10.1136/bmjopen-2018-02250.

[25] CatSalut, 2016. Riscos de fàrmacs que empitjoren la funció cognitiva en gent gran: hipnosedants, anticolinèrgics i estatines (juliol 2016). http://medicaments.gencat.cat/ca/professionals/seguretat/fitxes-seguretat/riscos-de-farmacs-que-empitjoren-la-funcio-cognitiva-en-gent-gran-hipnosedants-anticolinergics-i-estatines/

[26] Dublin S, Walker RL, Jackson ML, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: A population-based case–control study. J Am Geriatr Soc 2011;59:1899-907. doi:10.1111/j.1532-5415.2011.03586.x. https://doi-org.are.uab.cat/10.1111/j.1532-5415.2011.03586.x

[27] Wiese AD, Griffin MR, Schaffner W, et al. Opioid analgesic use and risk for invasive pneumococcal diseases: A nested case-control study. Ann Intern Med 2018;168:396-404. doi:10.7326/M17-1907. https://annals.org/aim/fullarticle/2672601/opioid-analgesic-use-risk-invasive-pneumococcal-diseases-nested-case-control

[28] Vozoris NT, Wang X, Fisher HD, Bell CM, et al. Incident opioid drug use and adverse respiratory outcomes among older adults with COPD. Eur Respir J2016;48:683-93. https://www.ncbi.nlm.nih.gov/pubmed/27418553

[29] CDC, 2019. Annual surveillance report of drug-related risks and outcomes — United States surveillance special report. Atlanta, GA: US Department of Health and Human Services, CDC; 2019. https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdfpdf iconhttps://www.cdc.gov/mmwr/volumes/69/wr/mm6911a4.htm?s_cid=mm6911a4_w

[30] Hider-Mlynarz K, Cavalié P, Maison P. Trends in analgesic consumption in France over the last 10 years and comparison of patterns across Europe. Br J Clin Pharmacol2018;84 1324-34. https://doi.org/10.1111/bcp.13564https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.13564

[31] CatSalut, 2017. Riscosassociats a l'ús concomitant d'opioides i benzodiazepines. http://medicaments.gencat.cat/ca/professionals/seguretat/fitxes-seguretat/Riscos-associats-a-lus-concominant-dopioides-i-benzodiazepines/

[32] Zeng C, Dubreuil M, LaRochelle MR, et al. Association of tramadol with all-cause mortality among patients with osteoarthritis. JAMA 2019;321:969-82. doi:10.1001/jama.2019.1347. https://jamanetwork.com/journals/jama/fullarticle/2727448

[33] Jeong S, Tchoe HJ, Shin JY. All-cause mortality associated with tramadol use: a case-crossover study. Drug Safety 2019;42:785-96. https://link.springer.com/article/10.1007/s40264-018-00786-y

[34] Taipale H, Tolppanen A-M, Koponen M, et al. Risk of pneumonia associated with incident benzodiazepine use among community-dwelling adults with Alzheimer disease. Can Med Assoc J 2017;189:E519-E529. doi:10.1503/cmaj.160126

[35] Obiora E, Hubbard R, Sanders RD, Myles PR. The impact of benzodiazepines on occurrence of pneumonia and mortality from pneumonia: a nested case-control and survival analysis in a population-based cohort. Thorax 2013;68:163-70. doi:10.1136/thoraxjnl-2012-202374 https://thorax.bmj.com/content/68/2/163

[36] Simó Miñana J. Uso de psicofármacos en España y Europa (2000-2015), 2018. http://saludineroap.blogspot.com/2018/04/uso-de-psicofarmacos-en-espana-y-europa.html. (Accessed 28 March 2020)..

[37] CatSalut, 2016. Riscos associats a l'ús simultani de diversos psicofàrmacs en gent gran (I). http://medicaments.gencat.cat/ca/professionals/seguretat/fitxes-seguretat/riscos-associats-a-lus-simultani-de-diversos-psicofarmacs-en-gent-gran-I-desembre-16/

[38] Vozoris NT, Wang X, Austin PC, et al. Serotonergic antidepressant use and morbidity and mortality among older adults with COPD. Eur Respir J 2018;52:1800475. doi:10.1183/13993003.00475-2018 https://erj.ersjournals.com/content/52/1/1800475

[39] Iacobucci G. NHS prescribed record number of antidepressants last year. BMJ 2019;364:l1508. doi:https://doi.org/10.1136/bmj.l1508https://www.bmj.com/content/364/bmj.l1508

[40] U.S. Food and Drug Administration. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). 30 January 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin (Accessed 29 March 2020).

[41] Gabapentin and risk of severe respiratory depression. Drug and Therapeutics Bulletin. 2018;56:3-4. doi:10.1136/dtb.2018.1.0571. http://dx.doi.org/10.1136/dtb.2018.1.0571

[42] European Medicines Agency, 2017. PRAC recommendations on signals [online]. http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2017/06/WC500229504.pdf (Accessed 27 March 2020).

[43] European Medicines Agency. SPC Lyrica. https://www.ema.europa.eu/documents/product-information/lyrica-epar-product-information_en.pdf. (Accessed 27 March 2020).

[44] Goodman CW, Brett AS. A clinical overview of off-label use of gabapentinoid drugs. JAMA Intern Med 2019;179:695-701. doi:10.1001/jamainternmed.2019.0086.

[45] Attal N, Barrot M. Is pregabalin ineffective in acute or chronic sciatica? N Engl J Med 2017;376:1169-70. https://www.nejm.org/doi/full/10.1056/NEJMe1701147

[46] Mathieson S, Chiro M, Maher CG, et al. Trial of pregabalin for acute and chronic sciatica. N Engl J Med 2017;376:1111-20. https://www.nejm.org/search?q=376%3A1111

[47] Johansen ME. Gabapentinoid use in the United States 2002 through 2015. JAMA Intern Med 2018;178:292-94. doi:10.1001/jamainternmed.2017.7856. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2666788

[48] Goodman CW, Brett AS. Gabapentin and pregabalin for pain – Is increased prescribing a cause for concern? N Engl J Med 2017;377:411-14. doi:10.1056/NEJMp1704633. https://www.nejm.org/doi/full/10.1056/NEJMp17046333

[49] Montastruc F, Loo SY, Renoux C. Trends in first gabapentin and pregabalin prescriptions in primary care in the United Kingdom, 1993-2017. JAMA 2018;320:2149-95. doi:10.1001/jama.2018.12358. https://jamanetwork.com/journals/jama/fullarticle/2716548

[50] Ferrer-Argelés P, Rafaniello C, Sabaté M, et al. Cross-national comparison of antiepileptic drug use: Catalonia, Denmark and Norway, 2007-2011. EpidemiolBiostatPubl Health 2014;11:e9405-1-e9405-9. doi:https://doi.org/10.2427/9405. https://ebph.it/article/view/9405

[51] Ortiz de Landaluce L, Carbonell P, Asensio C, et al. Gabapentin and pregabalin and risk of atrial fibrillation in the elderly: A population-based cohort study in an electronic prescription database. Drug Safety 2018;41:1325-31. doi:10.1007/s40264-018-0695-6.

[52] U.S. Food and Drug Administration. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). 30 January 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin (Accessed 29 March 2020).

[53] Eom CS, Jeon CY, Lim JW, Cho EG, et al. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ 2011;183:310-19. doi:https://doi.org/10.1503/cmaj.092129

[54] Lambert AA, Lam JO, Paik JJ, et al. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. PLoS One 2015;10:e0128004. doi:10.1371/journal.pone.0128004. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0128004

[55] Othman F, Crooks CJ, Card TR. Community acquired pneumonia incidence before and after proton pump inhibitor prescription: population based study. BMJ 2016;355:i5813. doi:https://doi.org/10.1136/bmj.i5813

[56] Herzig SJ, Doughty C, Marchina S, et al. Acid-suppressive medication use in acute stroke and hospital-acquired pneumonia. Ann Neurol 2014;76:712-18. https://onlinelibrary.wiley.com/doi/abs/10.1002/ana.24262

[57] Bateman BT, Bykov K, Choudhry NK, et al. Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study. BMJ 2013;347:f5416. https://doi.org/10.1136/bmj.f5416

[58] Lassalle M, Le Tri T, Bardou M, et al. Use of proton pump inhibitors in adults in France: a nationwide drug utilization study. Eur J Clin Pharmacol 2020;76:449-57. https://doi.org/10.1007/s00228-019-02810-1

[59] Othman F, Card TR, Crooks CJ. Proton pump inhibitor prescribing patterns in the UK: a primary care database study. PharmacoepidemiolDrug Safety 2016;25:1079-87. https://doi.org/10.1002/pds.4043

[60] CatSalut, 2015. Inhibidors de la bomba de protons idèficit de vitamina B12. http://medicaments.gencat.cat/ca/professionals/seguretat/fitxes-seguretat/inhibidors-de-la-bomba-de-protons/

[61] Pottegård A, Broe A, Hallas J et al. Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study. Ther Adv Gastroenterol 2016;9:671-78. https://doi.org/10.1177/1756283X16650156

[62] Hálfdánarson ÓÖ, Pottegård A, Björnsson ES, et al. Proton-pump inhibitors among adults: a nationwide drug-utilization study. Ther Adv Gastroenterol 2018;11:1756284818777943. https://doi.org/10.1177/1756284818777943

[63] Wright AA, Zhang B, Keating NL, et al. Associations between palliative chemotherapy and adult cancer patients' end of life care and place of death: prospective cohort study. BMJ 2014;348:g1219. doi:https://doi.org/10.1136/bmj.g1219

[64] Qian CJ, Coulomb J, Suissa S, Ernst P. Pneumonia risk in asthma patients using inhaled corticosteroids: a quasi-cohort study. Br J Clin Pharmacol 2017;83:2077-86. https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.13295

[65] Agencia Española de Medicamentos y Productos Sanitarios, 2016. Revisión sobre el riesgo de neumonía asociado a la administración de corticoides inhalados para el tratamiento de la EPOC. 18 March 2016. http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/2016/docs/NI-MUH_FV_06-corticoides.pdf

[66] CatSalut, 2016. Estimulants ß-adrenèrgics de llarga durada en el tractament de l'asma en nens. http://medicaments.gencat.cat/ca/professionals/seguretat/fitxes-seguretat/estimulants-adrenergics-de-llarga-durada-en-el-tractament-de-lasma-en-nens/

[67] Suissa S, Coulombe J, Ernst P. Discontinuation of inhaled corticosteroids in COPD and the risk reduction of pneumonia. Chest 2015;148:1177. doi: 10.1378/chest.15-0627. https://www.ncbi.nlm.nih.gov/pubmed/26110239

[68] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020:11. doi:https://doi.org/10.1016/S2213-2600(20)30116-8

[69] American Heart Association, Heart Failure Society of America, American College of Cardiology. American Heart Association webpage 2020:1 https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their-physician

[70] Dublin S, Walker RL, Jackson ML, et al. Use of opioids or benzodiazepines and risk of pneumonia in older adults: a population-based case-control study. Pharmacoepidemiol Drug Safety 2012;21:1173-82.

doi: 10.1111/j.1532-5415.2011.03586.x. https://onlinelibrary-wiley-com.are.uab.cat/doi/10.1002/pds.3340

[71] Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ 2020;368:m1086. https://www.bmj.com/content/368/bmj.m1086

[72] Ioannidis JPA. A fiasco in the making? As the coronavirus pandemic takes hold, we are making decisions without reliable data. STAT Daily Recap 17 March 2020. https://www.statnews.com/2020/03/17/a-fiasco-in-the-making-as-the-coronavirus-pandemic-takes-hold-we-are-making-decisions-without-reliable-data/

[73] Starko KM. Salicylates and pandemic influenza mortality, 1918–1919 Pharmacology, pathology, and historic rvidence. Clin Infect Dis 2009;49:1405-10. https://doi.org/10.1086/606060

[74] Gau JT, Acharya U, Khan S, Heh V, et al. Pharmacotherapy and the risk for community-acquired pneumonia. BMC Geriatr 2010;10:45. https://doi.org/10.1186/1471-2318-10-45

[75] Wang P, Wang Q, Li F, Bian M, Yang K. Relationship between potentially inappropriate medications and the risk of hospital readmission and death in hospitalized older patients. Clin Interv Aging 2019;14:1871-78. doi:10.2147/CIA.S218849. eCollection 2019. doi:10.2147/CIA.S218849https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6839805/

[76] Montané E, Arellano AL, Sanz Y, et al. Drug-related deaths in hospital inpatients: A retrospective cohort study. Br J Clin Pharmacol 2018; 84:542-52. doi:10.1111/bcp.13471.

[77] CatSalut, 2016. Riscos associats a l'ús simultani de diversos psicofàrmacs en gent gran (II). http://medicaments.gencat.cat/ca/professionals/seguretat/fitxes-seguretat/riscos-associats-a-lus-simultani-de-diversos-psicofarmacs-en-gent-gran-II-desembre-16/

[78] Healy D, Howe G, Mangin D, Le Noury J. Sudden cardiac death and the reverse dodo verdict. Int J Risk & Safety Med 2014;26:71-79. doi:10.3233/JRS-140615. https://www.researchgate.net/publication/262927140_Sudden_cardiac_death_The_Reverse_Dodo_Verdict